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Accounting for genetic and environmental confounds in associations between parent and child characteristics : a systematic review of children-of-twins studies

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Abstract

Parental psychopathology, parenting style, and the quality of intra-familial relationships are all associated with child mental health outcomes. However, most research can say little about the causal pathways underlying these associations. This is because most studies are not genetically informative and are therefore not able to account for the possibility that associations are confounded by gene-environment correlation. That is, biological parents provide not only a rearing environment for their child but also contribute 50% of their genes. Any associations between parental phenotype and child phenotype are therefore potentially confounded. One technique for disentangling genetic from environmental effects is the Children-of-Twins (CoT) method. This involves using datasets comprising twin parents and their children to distinguish genetic from environmental associations between parent and child phenotypes. The CoT technique has grown in popularity in the last decade and we predict that this surge in popularity will continue. In the present article we explain the CoT method for those unfamiliar with its use. We present the logic underlying this approach, discuss strengths and weaknesses and highlight important methodological considerations for researchers interested in the CoT method. We also cover variations on basic CoT approaches, including the extended-CoT method, capable of distinguishing forms of gene-environment correlation. We then present a systematic review of all of the behavioral CoT studies published to date. These studies cover such diverse phenotypes as psychosis, substance abuse, internalizing, externalizing, parenting and marital difficulties. In reviewing this literature we highlight past applications, identify emergent patterns, and suggest avenues for future research.

Keywords: children-of-twins; gene-environment correlation; intergenerational transmission; parenting; psychiatric epidemiology.

Theories of parenting propose that parents impact the development of their children in a variety of ways: At one level parental characteristics are predictive of child characteristics – many traits tend to run in families and this is often interpreted as evidence for the impact of parent behavior on child development. For example, anxious parents often rear anxious children (Murray et al., 2008) and it has been suggested that this is because children learn such behavior from their parents (Murray et al., 2008; Rachman, 1977; 1991). Proponents of social learning theory (Bandura, 1977) might suggest that this learning occurs via processes of imitation and modelling, and evidence also indicates that the learning process can be more direct and involve the verbal transmission of information from parent to child (Field & Purkis, 2011).

Although children may learn behaviors through imitating and listening to their parents, parents often seek to influence their children's behavior in more direct ways, through the parenting behaviors that they direct towards their child. For example, the punishment and praise of children can be viewed as attempts at conditioning and reinforcement: If the child learns to associate certain behaviors with punishment then they will be motivated to avoid such behaviors. If they associate other behaviors with rewards then those behaviors may become more commonplace. Beyond attempts at the operant conditioning of specific behaviors, various parenting practices have been associated with child outcomes. For example, parental monitoring is consistently associated with reduced levels of adolescent externalizing behaviors (Dishion & McMahon, 1998; Laird, Criss, Pettit, Dodge & Bates, 2008), and harsh parental discipline is associated with elevated levels of all types of psychopathology (Gershoff, 2002). As well as associations between specific parenting *practices* and child outcomes, researchers such as Baumrind (1966) and others (e.g. Maccoby & Martin, 1983) have linked parenting *style* with a host of child outcomes including personality, educational achievement, and psychopathology. For example, authoritarian parenting (a strict, punitive parenting style, characterized by expectations of conformity and compliance) is associated with offspring conduct problems (Thompson, Hollis & Richards, 2003), whereas a parenting style

comprising parental warmth and positive expressivity is associated with effortful control and reduced externalizing problems in children (Eisenberg et al., 2005).

When considering relationships between parenting and child outcomes the direction-of-effect is often conceptualised as running from parent to child. However, Bell (1968; 1979) and others (Belsky, 1984; Schneewind, 1989) have highlighted the existence of child-to-parent effects, whereby child behavior may impact upon the parenting that they receive just as parenting can impact child behavior. Subsequent research has shown that the relationship between parenting and child outcome is often reciprocal, with each affecting the other over time (e.g. Anderson, Lytton & Romney, 1986; Cecil, Barker, Jaffee & Viding, 2012; Lytton, 1990). Indeed, parenting can be viewed as a social interaction between parent and child, so researchers should always test for the possibility of bidirectional effects between parent and child where possible.

Beyond the parents' personality traits, parenting style and parenting practices, theorists also propose that other elements of the family environment impact upon child development. Belsky (1984), Caldwell and Bradley (1984) and others (Bronfenbrenner, 1979; Schneewind, 1989) have all noted that phenomena such as the organisation of the home environment, the provision of play materials, and the marital relations of parents all go into making up the family environment and all may impact child development. Empirical examples include the link between the degree of chaos within a household and children's problem behavior (Coldwell, Pike & Dunn, 2006), the association between the use of violent video games and increased aggression and reduced empathy (Anderson, 2010), and reports that children whose parents are divorced or separated may be prone to elevated emotional and behavioral problems compared to their peers (Amato 2001; Amato & Keith, 1991).

The Confounding Effects of Genetic Relatedness

When focussing on the role that parents may play in child development, parent behavior, parenting style and the family environment are typically conceptualised as components of the 'rearing

environment'. That is, something external to the child that impacts on the child's development in what is often presumed or implied to be a causal manner. However, behavioral geneticists would point out that because parents share 50% of their genes with their children, associations between parent and child behavior could reflect genetic transmission as well/instead of environmental transmission (i.e. learning) (Eaves, Last, Martin & Jinks, 1977; D'Onofrio et al., 2003; Rutter, Pickles, Murray & Eaves, 2001; Rutter et al., 1997). It is worth noting here that this does not only apply to associations between the same phenotype (e.g. the association between parental depression and offspring depression). The 'generalist genes hypothesis' makes it clear that genes can affect multiple traits, or 'phenotypes' (Eley, 1997; Plomin & Kovas, 2005). As such correlations between conceptually distinct phenotypes may arise as a result of shared genes. For example, in the study of psychopathology it has become clear that all forms of psychopathology share common variance via a single general psychopathology dimension (the 'p' factor: Caspi et al., 2013; Lahey et al., 2012; Pettersson, Anckarsäter, Gillberg, Lichtenstein, 2013). Such higher order factors have been found to be highly heritable (e.g. Andrews et al., 2009; Krueger et al., 2002), meaning that genetic overlap is often identified as a major cause for correlations between different traits. This genetic pleiotropy means that *any* association between a parental measure and child outcome is potentially confounded: Parents and children share genes so if there is overlap in, for example, the genes involved in child conduct problems and those involved in harsh parental discipline then we cannot know whether there is truly an effect of harsh discipline on conduct problems (or vice versa) without first accounting for that genetic overlap. If there is overlap and we do not account for it then any relationship between a parental measure and a child outcome will be at best inflated and at worst spurious. That is, there could actually be no causal environmental pathway from the parental characteristic to child outcome. Not accounting for this can therefore lead researchers to make incorrect conclusions. As discussed above, several developmentalists have also noted that relationships between parenting and offspring behavior can be reciprocal – child behavior impacting parenting style is as feasible an explanation for many associations as the notion that parenting style

impacts child behavior (e.g. Bell, 1968; 1979; Belsky, 1984; Schneewind, 1989). Whether the apparent direction of effects is parent-to-child or child-to-parent the genetic relatedness of parent and child means that such relationships are all potentially confounded.

This issue of genetic involvement in putative environmental variables is known as gene-environment correlation. Gene-environment correlation (rGE) can be defined as a correlation between an individual's genome and the environment that they inhabit. In the field of behavioral genetics several decades of genetically informative research have shown rGE to be a ubiquitous phenomenon and common source of confound (Jaffee & Price, 2007; Kendler & Baker, 2007; Plomin, De Fries & Loehlin, 1977; Plomin & Bergeman, 1991). Three forms of rGE have been described: passive, active and evocative (Plomin, Defries, & Loehlin, 1977; Scarr & McCartney, 1983). Passive rGE describes the association between a child's genotype and the environment in which they are raised, both of which are provided by the child's biological parents. Active rGE involves the genetically influenced behavior of the child seeking out an environment that 'matches' their genotype. Evocative rGE involves the genetically influenced behavior of the child seeking or evoking a particular response from the environment. It is easy to see how each of these forms of rGE could potentially confound associations between parent phenotype (i.e. the child's "environment") and child phenotype. For example, a child may inherit genetic factors involved in conduct problems from their parent in whom the same genetic factors may be involved in harsh parental discipline, an example of passive rGE confounding the association between conduct problems and harsh parental discipline. Another example might involve the child's genetically influenced conduct problems leading them to actively seek confrontation with their parent (active rGE), or to evoke harsh discipline from their parent (evocative rGE). If those genes involved in conduct problems in the child were also involved in harsh discipline in the parent, then this would confound the association between conduct problems and harsh parental discipline.

Many ostensibly environmental aspects of the rearing 'environment' are subject to genetic influence. This includes parental characteristics, parenting style (Perusse, Neale, Heath & Eaves, 1994; Wade & Kendler, 2000), parent-child relationships (Elkins, McGue & Iacono, 1997; McGue, Elkins, Walden & Iacono, 2005; Neiderhiser et al., 2004; Neiderhiser, Reiss, Lichtenstein, Spotts & Ganiban, 2007), and the structure and organization of the home environment (Saudino & Plomin, 1997). Evidence from twin studies (McAdams, Gregory & Eley, 2013; Narusyte et al., 2008; 2011; Pike et al., 1996; Saudino & Plomin, 1997) demonstrate that the genetic factors associated with these elements of the rearing environment correlate with those involved in offspring psychopathology. As such any associations between these variables and measures of child outcome may be subject to the confounding effects of rGE. That is, despite being correlated *there may be no causal link between them*.

Getting an accurate picture of which of the relationships between parent and child phenotypes are confounded and which are not is crucial because manipulating the rearing environment may provide a mechanism through which parents and practitioners can have a positive impact on the development of children. This is not to say that those components of the rearing environment that are under genetic influence are not important to child development or not amenable to intervention. As discussed, gene-environment correlation is ubiquitous and genetic influence on a phenotype should not be taken to imply that it cannot be changed. However, identifying those relationships between the rearing environment and child phenotypes that are strong in effect and least confounded by background familial factors is likely to prove a useful tactic in the design of successful interventions.

Behavioral scientists employ a variety of methods to account for confounds. Examples from the experimental tradition typically involve the random allocation of participants to conditions. For example, many researchers have assessed randomised control trials of parenting interventions aimed at improving child well-being or behavior. Where such trials are effective this can give

researchers insight into which parenting behaviors impact children's behavior independent of confounds accounted for by the randomisation process (e.g. Gardner, Burton & Klimes, 2006; Kaminski, Valle, Filene & Boyle, 2008). Alternatively researchers can employ naturally occurring quasi-experiments involving groups of individuals that differ in their genetic and/or environmental relatedness (for reviews of the many research designs capable of controlling for familial confounds see D'Onofrio & Lahey, 2010; D'Onofrio, Lahey, Turkheimer, Lichtenstein, 2013; Horwitz & Neiderhiser, 2011; Rutter, Pickles, Murray & Eaves, 2001). That is, the degree to which their genome and environment correlate. For example, twin studies involve dyads or clusters of individuals who differ in their genetic/environmental relatedness: Identical twins share all of their genes, whereas fraternal twins share 50% of their segregating genes. By using carefully designed genetically informative datasets that involve individuals from both the parent and the child generation it is possible for researchers to distinguish between genetic and environmental transmission from parent to child.

In the present review we focus exclusively on the children-of-twins (CoT) design. The CoT method involves using samples of twins who themselves have children. CoT studies have risen in popularity in the last decade as more and more twin samples have come to an age at which they are having children of their own. Several parent-child relationships have now been examined using this method, but many more remain. With an increasing number of twin samples entering adulthood, and thus increasing opportunities for scientists to employ the CoT method in their research, this is an ideal time for a review of the extant CoT literature.

The Children-of-Twins Method

In the present article we describe the CoT method and its variants, describe the logic underlying this approach, discuss its strengths and weaknesses, and highlight methodological considerations of importance to those considering employing CoT techniques in their research. In order to demonstrate the utility of CoT samples and document past uses we follow our review of the CoT

method with a systematic review of empirical CoT studies that have examined the effects of the family environment on child development, the impact of parenting practises, and the nature of the intergenerational transmission of psychopathology. In our review we highlight findings of interest, suggest possible directions for future CoT studies and discuss some of the problems encountered in CoT studies to date. It is our intention that this review can serve to guide researchers in their use of CoT data when examining relationships between parent phenotypes and child phenotypes.

The Logic of the Children-of-Twins Method

Following biometrical genetic theory we can describe the genetic relatedness between two people in terms of the proportion of genetic variance that they share on average (Neale & Cardon, 1992; Plomin, DeFries, Knopik & Neiderhiser, 2013; Rijdsdijk & Sham, 2002). A child receives 50% of their DNA from each parent and thus shares .50 of their genetic variance with either parent. Siblings with the same parents share on average .50 of their genetic variance with each other, half-siblings .25, cousins .125 and so on. Dizygotic (DZ) twins share on average .50 of their genetic variance, while monozygotic (MZ) twins are unique in that they share 100% (1.00) of their genes. As a result *the offspring of MZ twins are as genetically related to their parents' co-twin as they are to their own parent* (.50). This quirk of nature or quasi-experiment gives researchers a unique opportunity to distinguish between genetic and environmental transmission from one generation to the next (D'Onofrio et al., 2003; Fischer, 1973; Heath, Kendler, Eaves, & Markell, 1985; Nance & Corey, 1976; Silberg & Eaves, 2004). In Figure 1 we present a simple path diagram showing the different genetic relationships within MZ twin families and DZ twin families. As can be seen the children of MZ twins are also more related to one another than are typical cousins; .25 compared to .125 (these cousins are as related as half siblings).

>>Insert Figure 1 around here

Not only genetic factors make family members alike. Some environmental effects serve to make family members similar to one another as well. The 'shared environment' is a title given collectively to non-genetic factors that make members of a nuclear family similar to one another (Neale & Cardon, 1992). For example, the correlation between siblings or between parent and child may be explained by both genetic and shared environmental factors. Beyond those environmental effects common to members of a nuclear family, there may also be environmental effects common to members of an extended family. For example, the correlation between two cousins, or between an uncle and a nephew can be attributed to shared genes and/or the environmental effects common to their extended family (Heath et al., 1985). These shared environmental effects tend to be estimated as far smaller in magnitude than genetic effects but they also comprise a source of confounding when examining correlations between parent and offspring generations. Importantly CoT analyses are capable of accounting for the confounding effects of the shared familial environment as well as genetic confounds. In Table 1 we summarise how genetic and environmental effects are shared for a variety of familial relationships (dyads).

>>Insert Table 1 around here

Analysing COT Data

The earliest examples of CoT studies involved the analysis of the families of MZ twins only (Fischer, 1971; Magnus, Berg & Bjerkedal, 1985; Nance, Kramer, Corey, Winter & Eaves, 1983). Nance & Corey (1976) were the first to fully articulate a method for the analysis of such families. As with modern techniques, this method decomposes intergenerational covariance into that attributable to genetic and environmental factors. This is done by making comparisons between parent-offspring and avuncular correlations (correlations between aunt/uncle and niece/nephew). The former can be attributed to a combination of exposure to parental phenotype and familial factors (genetic and environmental), whereas the latter can be attributed to familial factors only. Thus, if the parent-offspring correlation is significantly greater than the avuncular correlation then this indicates the

presence of an effect of exposure above and beyond that attributable to familial confounds.

Although the use of MZ twin families can inform us of the nature of intergenerational relationships and, in theory, the etiological structure of offspring phenotype (through comparisons of correlations, between/within sib-ships and cousins who are genetically half-siblings), this design lacks the information necessary to calculate the etiological structure of parent phenotype. That is, in the parent generation it is not possible to distinguish environmental effects that make twins alike from genetic effects (either could be responsible for correlations within MZ twin pairs).

CoT analyses involving both MZ and DZ twin families are able to estimate the etiological structure of parent phenotype (D'Onofrio et al., 2003; Heath et al., 1985; Magnus et al., 1985). Including more twin pairs also increases power to detect other parameters (e.g. intergenerational pathways and offspring etiology), and the inclusion of DZ twins increases the generalizability of results. CoT studies including MZ and DZ families rely on comparisons of the relative magnitude of a series of intra-familial correlations. Table 2 represents several such correlations. By making comparisons between MZ and DZ correlations we are able to estimate the etiological structure of the parental phenotype and the child phenotype as well as the phenotypic relationship between the two.

>>Insert Table 2 around here

In Table 2, the difference between correlations MZpp (that between parent 1 and parent 2) and DZpp contains information regarding the etiological structure of the parental phenotype. If the MZ correlation is higher than the DZ correlation then this is indicative of genetic effects on the parental phenotype (this is the standard twin model as described elsewhere: Neale & Cardon, 1992; Rijdsdijk & Sham, 2002). Similarly the difference between correlations MZcc (that between child 1 and child 2) and DZcc contains information regarding the structure of the child phenotype. Correlations between parent and child phenotypes (MZpc, DZpc) represent phenotypic relations between parental phenotype and child phenotype. Differences in avuncular correlations (between MZav and DZav) highlight the possible mechanisms of intergenerational transmission: If the MZav correlations are

higher than the DZav correlations then this is indicative of genetic transmission. This is because MZ avuncular relationships are characterised by stronger genetic relatedness than DZ avuncular relationships, so any differences can be attributed to genetic factors. If there are no differences between MZ avuncular correlations compared to DZ avuncular correlations then this suggests that genetic transmission is not taking place. If the parent-child correlations (MZpc, DZpc) are larger than the respective avuncular correlations (MZav, DZav), this suggests an effect of parent phenotype on offspring phenotype above and beyond familial confounding. Broadly, there have been 3 analytical techniques adopted by contemporary CoT researchers; between-families comparisons, hierarchical linear modelling and structural equation modelling.

Between Families Comparisons

The simplest approach to analysing CoT data involves the grouping of offspring into risk categories, dependent upon the level of genetic and environmental risk they have been exposed to. Comparisons can then be made using appropriate statistical tests (means comparisons, odds ratios etc.) with covariates and control variables included in models. This method is well suited to data in which the parental phenotype is dichotomous (such as psychiatric diagnosis). An example of this kind of analysis can be taken from Haber et al. (2005). They used the presence or absence of alcohol dependence in twins (parents) to index four groups of offspring: 1) Those whose parents were affected (exposed to parental alcoholism and at high risk from familial factors); 2) those with an unaffected parent, but affected MZ co-twin (not exposed to parental alcoholism but at high risk from familial factors); 3) unaffected parent, affected DZ co-twin twin (not exposed to parental alcoholism but at moderate risk from familial factors); 4) unaffected parent, unaffected co-twin (not exposed to parental alcoholism and at low risk from familial factors). Differences between groups (or the lack thereof) can be used to infer whether associations between parent and child phenotypes are genetic or environmental in nature. For example, if group 2 (high familial risk, no exposure) scored significantly *lower* than group 1 (high familial risk, exposed to parental alcoholism) on an outcome of

interest then this would indicate that parental alcoholism predicts child outcome above and beyond familial risk. Note that this comparison is equivalent to comparing an MZ avuncular correlation with an MZ parent-child correlation. If prevalence rates in group 2 (high genetic risk, no exposure) are higher than in group 3 (moderate genetic risk, no exposure) then this would indicate genetic effects. This is equivalent to comparing MZ and DZ avuncular correlations. It is worth noting here that the ability of this approach to meaningfully distinguish potential causal effects from familial confounds is entirely dependent on comparisons between the offspring of discordant twin pairs. As such, it is important that a reasonable proportion of the sample are discordant on the parental phenotype. For highly heritable phenotypes this may require selective sampling.

Hierarchical Linear Models

Hierarchical linear modelling (HLM; also referred to as multilevel modelling or the modelling of nested models) is often applied to CoT data. HLM is a regression-based approach capable of accounting for the complex data structure of individual offspring nested within nuclear families, nested within twin families. HLM of CoT data can include a range of covariates and control variables. Being regression-based, different estimators can be used in HLM, dependent on the type of data being analysed. As such HLM has often been applied when researchers have been investigating dichotomous or categorical variables (such as psychiatric diagnosis).

HLM involves fitting a series of regression models, each one aimed at assessing the association between parent and child phenotypes at different levels of the analysis and/or with different covariates included. Of particular interest to the distinction between genetic and environmental confounds and potential causal effects are the within-twin-family effects, or cousin comparisons. Cousins share genetic and environmental familial confounds so if differences in parental phenotype predicts differences in offspring phenotype then this indicates that the effect of parent on child persists after controlling for familial confounds. The presence of within-twin-family effects in MZ twin families provides the most rigorous test of an environmental effect of parent on child. By

comparing the strength of this effect with that within DZ twin families it is possible to test for the significance of genetic vs. environmental familial confounding. If the within-twin family association is greater in DZ families compared to MZ families then this implies that genetic confounding is present (because the effect is being attenuated to a greater extent in the MZ families, where genetic relatedness between cousins is greater). If the difference between MZ and DZ families is negligible then this would imply that genes are not the source of confounding, so any familial confounding must be environmental. HLM in CoT models is explained in greater detail elsewhere (D'Onofrio et al., 2005; Singh et al., 2011; Slutske et al., 2008).

Slutske et al. (2008) compared the between families comparisons approach with the within-family HLM approach and found that conclusions were comparable. However, they (and others: e.g. Harden et al., 2007) do point out that the HLM approach is the more sophisticated and provides greater scope for rigorous hypothesis testing by directly comparing cousins, as opposed to comparing groups of individuals at different levels of risk.

Structural Equation Models

Although between families comparisons and HLM are useful ways to deal with the complex structure of CoT data, they do not explicitly quantify latent genetic and environmental influences on phenotypes. Structural equation modelling can do this. In behavioral genetic research, structural equation models (SEMs) are used to decompose variance on a trait (or covariance between traits), into that attributable to genetic and environmental effects. Typically variance is decomposed into that attributable to additive genetic effects (A; genetic effects that operate in an additive manner), common or shared environment effects (C; environmental effects that make members of the same nuclear family more alike), and non-shared environment effects (E; environmental effects that make members of a family unit different to one another) (Neale & Cardon, 1992). By decomposing the covariance between parent phenotype and child phenotype, SEMs of CoT data can tell us the proportion of that covariance attributable to genetic and environmental effects.

Structural equation modelling of CoT data is most appropriate when parent and child phenotypes are normally distributed and continuous (although recent advances in several statistical software packages have greatly advanced the ability to analyse categorical and skewed variables). Several SEMs suitable for use with CoT data have been described (Heath, Kendler, Eaves, & Markell, 1985; Nance & Corey, 1976; Narusyte et al., 2008; Silberg & Eaves, 2004; Silberg, Maes, & Eaves, 2010).

One such model is reproduced in Figure 2 (Silberg et al., 2010). In this model not only are twins and their children included but the twins' spouses are also included. Because both parents are typically involved in providing a rearing environment for their child, the ability to incorporate both parents into models of intergenerational transmission is important.

>> Insert Figure 2 around here **(will need publisher's permission)**

A limitation of CoT models is that they do not account for the possibility that the child's phenotype may impact upon that of the parent's. Although this may make sense for some phenotypes (i.e. a child cannot affect its mothers smoking behavior prior to birth), the relationship between parenting and child outcome is often bidirectional (Bell, 1968; 1979; Burt, McGue, Krueger, & Iacono, 2005; Cecil, Barker, Jaffee, & Viding, 2012; Neiderhiser et al., 2004; 2007). That is, the parenting style adopted by parents may affect their child AND the behavior of a child may affect his/her parents' parenting style. In response to this limitation, the Extended Children-of-Twins (ECoT) model was designed - a model capable of accounting for bidirectional associations between parent and child phenotypes (Narusyte et al., 2008). A major strength of this model is that because parent-to-child and child-to-parent effects are both estimated it is possible to distinguish between passive rGE (where parents provide their children with genes and a correlated rearing environment) and active/evocative rGE (where the child's genetically influenced behavior leads to them actively seeking/evoking a correlated environment)¹. Because standard CoT models only estimate parent-to-

¹ Active and evocative rGE are statistically indistinguishable in these designs because they are both 'child-driven'.

child effects, child-to-parent effects will be subsumed into the parent-to-child estimate, meaning that all genetic confounding appears as passive rGE. As such evocative rGE may be mislabelled as passive rGE. Where the genes involved in child behavior do not overlap with those involved in the twins parenting, then evocative rGE will go unnoticed.

In order to accurately detect active/evocative rGE it is necessary to estimate genetic effects on offspring phenotype. Typical CoT datasets have only low power to do this. This is because child specific genetic effects are estimated based on the difference between MZ offspring and DZ offspring correlations. The difference in genetic relatedness between these types of cousin is small (.25 compared to .125), and considerably smaller than in the parental (twin) generation (1.00 compared to .50). In order to increase the power to detect genetic effects on offspring phenotype ECoT studies introduce a second dataset into the model - one comprising twin children and their parents (Narusyte et al., 2008). In such a sample power to detect child specific genetic effects is greatly increased, relying as it does on MZ genetic correlations of 1.00 and DZ correlations of .50. Thus, an ECoT study involves using 2 samples with overlapping measures that both provide information with which a SEM is constructed. In one sample the parents are twins and their offspring are cousins with one another. In the other sample, the children are twins and they share a parent (who reports on their parenting behavior as directed at each child separately). The former sample enables the estimation of genetic and environmental effects on parenting. The latter gives the power required to estimate genetic and environmental effects on the child phenotype. Both contribute to the estimation of bidirectional pathways. The ECoT model is reproduced in Figure 3. Further details are given in Narusyte et al. (2008).

Neiderhiser et al. (2004) discuss how comparisons between univariate estimates of the etiological structure of parenting across parent and child twin samples can inform as to the presence and nature of any rGE. For example, they point out that genetic influences on parenting in a child-based twin sample would indicate that the child's genes influence parenting – indicative of active or

evocative rGE. This interpretation would be further substantiated if parent genes were not found to be important in a parent-based twin sample. In the absence of evocative gene-environment correlation, parents will treat their children the same, regardless of their children's genetic relatedness. In such a situation parenting will be estimated as being under the influence of the shared environment when assessed in child-twin samples. If, in the parent-twin sample parenting is then estimated as being under genetic influence then this would be consistent with passive rGE, meaning that parental genes drive parenting but parenting is consistent across children.

>> Insert Figure 3 around here (**will need publisher's permission**)

It is worth highlighting here that the ECoT model described above was designed to assess bidirectional relationships between offspring phenotype and *parenting*, and not relationships between offspring phenotype and parent phenotype. That is, although this model can assess bidirectional relationships between, for example, harsh parenting and offspring conduct problems, it cannot be used to assess bidirectional relationships between parent antisocial behavior and offspring conduct problems. This is because in the 'twins-as-children' component of the model, the same parent is used for twin 1 and twin 2. Thus, while parenting can vary between twins, parent characteristics will not. As such, if a parent characteristic such as antisocial behavior were used in an ECoT model, twin 1 and twin 2 in the children-as-twins group would have exactly the same 'parent antisocial behavior' score, leading to problems of multicollinearity. We have explored the possibility of creating a model capable of assessing bidirectional effects between parent and child phenotype, but this does not appear to be possible using cross-sectional data. It is possible that future model development incorporating longitudinal CoT data will allow for the assessment of bidirectional relationships between parent and child phenotypes but such a model has not yet been developed.

Methodological Considerations in CoT Studies

When using CoT data, or when interpreting the results of CoT analyses, there are several considerations that should be taken into account (D'Onofrio et al., 2003; Eaves et al., 1978; Neiderhiser et al., 2007). First is the assumption of random mating. When information on the spouse is not included in analyses then the model implicitly assumes the absence of assortative mating. Assortative mating describes the situation in which mates select each other according to their similarity. Studies indicate that the assumption of random mating is incorrect for many externalizing phenotypes (Frisell, Pawitan, Langstrom, & Lichtenstein, 2012; Krueger, Moffitt, Caspi, Bleske, & Silva, 1998; Taylor, McGue, & Iacono, 2000), so where possible information on the spouse should be included in CoT models. This can be done by explicitly modelling the spouse's phenotype (see Figure 3), by regressing out the effects of spousal phenotype on twin (parent) phenotype, or by including spousal phenotype as a covariate in HLM.

Second, as in all studies employing the behavioral genetic twin method, CoT studies make the Equal Environments Assumption (EEA). In classical twin studies the EEA refers to the assumption that the environments of MZ twins are not substantially more similar to those of DZ twins (regarding environmental variables of etiological relevance to the phenotype under examination)². In CoT studies the EEA also involves the assumption that the offspring of MZ twin pairs are not influenced by their parent's co-twin any more than are the offspring of DZ twins. Any violation of this assumption would artificially inflate avuncular correlations within MZ families relative to DZ families, potentially leading to false conclusions regarding the importance of genes in intergenerational transmission. One possible route via which avuncular influence could be greater in MZ families relative to DZ families is through avuncular contact (time spent together/in contact with one another). If avuncular contact is greater in MZ families, and if contact predicts offspring outcome, then this would constitute a violation of the EEA. Fortunately this possibility can be directly estimated in CoT studies by measuring the amount of avuncular contact between the children and

² It is worth noting here that several researchers have systematically tested for violations of the EEA and none have reported any serious impact on heritability estimates (Hettema, Neale & Kendler, 1995; Kendler & Gardner, 1998; Kendler, Neale, Kessler, Heath & Eaves, 1993).

their aunt or uncle. Where the EEA is violated the amount of contact offspring have with their parents co-twin can be included as a covariate. At least one attempt to explicitly assess the EEA in a CoT sample has been reported (Koenig, Jacob, Haber, & Xian, 2010). In a sample of children of alcohol and drug dependent fathers and their co-twins and spouses (1,774 twin fathers, 1,202 mothers and 1,919 children in total) it was found that MZ twins had more contact with each other than did DZ twins. However, using twin contact as a proxy measure for avuncular contact, the degree of contact was not predictive of child outcome (alcohol dependence, conduct disorder and nicotine dependence). Thus, although MZ twins have more contact than DZ twins, the degree of contact does not appear to affect child outcomes in such a way that would invalidate the conclusions drawn from CoT studies.

Third, because cousins are typically not the same age as one another, and because most phenotypes of interest (and the intergenerational relationships between phenotypes) are likely to change with age, it is necessary to control for age differences between cousins, and/or use specific sampling strategies to account for this (D'Onofrio et al., 2003). This may also apply to the age of the mother/father at the birth of their child.

Limitations of the CoT Design

The CoT design, like any other, is subject to limitations. First and foremost; although the CoT design controls for familial confounds (genetic and environmental) and thus has the potential to strengthen the case for arguments of causation between parental phenotype and offspring outcome, the CoT design **does not** enable researchers to make causal conclusions. This is because it is always possible that, despite controlling for familial confounds, associations between parent and offspring phenotype are confounded by other unmeasured variables. For example, if an association between parental alcoholism and offspring depression was found to remain after controlling for familial confounding, the association could still be explained via other confounding variables such as parental depression, offspring alcoholism, or maternal substance use during pregnancy (for this

reason twin/spouse smoking and drinking during pregnancy is frequently included as a control variable in CoT studies of parental alcoholism and substance use). Therefore wherever possible, CoT researchers should identify likely confounds and control for them.

As mentioned above under Methodological Considerations, it is important to include spousal information in CoT models where possible. However, even where this is possible, it is important to note that such information will only be informative at the phenotypic level – it will not be possible to distinguish genetic from environmental sources of variance on spousal phenotype. The effects of this limitation may be more or less important dependent upon the phenotypes under study. As explained by Eaves, Silberg and Maes (2005), of particular importance is the extent to which a phenotype is single- or multi-agent in nature. That is, whether it is best conceptualised as the phenotype of a single person (such as height), or the product of the interaction between people (such as discord within a relationship). Eaves et al. (2005) showed that if a variable is dyadic (e.g. divorce), and is affected by the genetic and environmental influences acting on both parents (twin and spouse) this can seriously impact the ability of the CoT model to distinguish genetic from environmental intergenerational transmission, even in randomly mating populations. To illustrate we can focus exclusively on MZ twin families: In a typical CoT design the phenotype of each parent is the result of genetic, shared environment and non-shared environment effects. In MZ families, genetic effects on each twin parent's phenotype correlate at 1.00, shared environment effects correlate at 1.00, and non-shared environment effects are not correlated at all. However, given that the spouse of each twin is likely to be unrelated, and given that each spouse also contributes genetic and environmental effects to the parental phenotype, we can no longer be sure that the genetic correlation between parental phenotypes (e.g. divorce) in MZ twin pairs will be 1.00 – we cannot know what the genetic correlation is at all. This is of course a substantial limitation for the application of the CoT design to dyadic parental phenotypes. As such it is important that researchers make efforts to define phenotypes in ways that ensure they are 'single-agent' wherever possible.

The ECoT model is subject to the above limitations but also has one of its own: Narusyte et al. (2008) note that estimating genetic *and* shared-environmental effects on both child and parent phenotypes leads to limited power to reject false causality hypotheses (see also Heath et al., 1993). As such they suggest not estimating C on parental phenotypes. This means that ECoT models should only be applied where the influence of C on the parenting phenotype is minimal³. In a bidirectional effects model it is also necessary to estimate error terms separately from the effects of non-shared environmental influences (the two are typically conflated in twin models) (Heath et al., 1993). In order to ensure that the model is identified these error terms must be constrained to be the same in parents and offspring. Although constraining error terms to be the same for parent and child is a limitation, estimating error terms separately from non-shared environment estimates does mean that the non-shared environment estimates in these models are potentially more interpretable than is usually the case with twin models, being as they are ostensibly free of error.

Throughout the CoT literature, problems with statistical power are often evident. Some of these problems relate primarily to the set up and design of the different models applied to CoT data. For example, CoT samples alone are not able to estimate nuclear shared environment effects on child phenotype and have very limited power to detect genetic effects on child phenotype. However, the primary purpose of CoT analyses is to decompose covariance between parent phenotype and child phenotype into that attributable to familial confounds (the sharing of genetic and environmental factors arising from being part of the same family) and the residual covariance that may be attributable to a direct environmental effect of parent phenotype on child phenotype and/or (in the

³ This issue is actually less problematic than it might first appear. Although many studies suggest that parenting does have a shared environment component, such studies are primarily child-twin studies, where the twins receive the parenting (e.g. Lichtenstein et al., 2003; Neiderhiser et al., 2004). Studies where the parents are the twins do not tend to find significant evidence for the shared environment on parenting (e.g. Neiderhiser et al., 2004; Perusse et al., 1994). Indeed, in their recent meta-analysis, Klahr & Burt (2013) found no evidence for shared environment effects on parent-reported parental warmth and negativity, and only small effects on parental control. Significant shared environment estimates would suggest that the rearing environment that twins shared as children impacts on their parenting practises as adults, and/or that current contact with their co-twin influences parenting similarity. In CoT models the information for estimating parental shared environment comes from the parent generation, not the child, so significant shared environment estimates should not typically be expected.

case of the ECoT model discussed above) vice versa. The ability to decompose covariance into these components is affected by three primary issues: First, the size of the phenotypic relationship – the smaller the relationship the less power there will be to meaningfully decompose it. Second is sample size – the greater the number of parent-child correlations then the more power there is to distinguish between familial confounds and phenotypic relationship. Third, the nature of the measures used – the use of categorical measures results in lower power than when compared to the use of normally distributed continuous variables. Power analyses and simulations have been reported elsewhere (e.g. Heath et al., 1985; Narusyte et al., 2008) but are specific to the models, measures and samples used so it is difficult to state here an ideal sample size that researchers should aim for. However, by inspecting the results reported in the extant literature we can say that studies that have encountered problems in distinguishing genetic from environmental effects have tended to be those using dichotomous phenotypes with samples comprising less than 800 twin pairs and their children.

Where power is low the confidence intervals on the decomposed components of the parent-child phenotypic relationship may overlap, making it impossible to distinguish one from the other (i.e. familial confounds from potential phenotypic effect) with any statistical certainty. This was an issue encountered by (amongst others) Slutske et al. (2008), who suggested that in such instances researchers should report confidence intervals and interpret point estimates, while acknowledging any lack of statistical significance. They point out that if power were to be increased then confidence intervals would likely narrow in on an estimate close to the point estimate itself. We would agree that (tentatively) interpreting point estimates is preferable to no interpretation whatsoever but of course without sufficient power it will not be possible to draw any firm conclusions. One group of CoT studies particularly affected by problems with low power are those investigating the effects of parental substance abuse and alcoholism on child outcome. One of the major reasons for this is likely to be the use of diagnostic categories to measure substance abuse. Because substance dependence and abuse are highly heritable (Hopfer, Crowley & Hewitt, 2003), twin pairs discordant

for substance use are relatively rare. As such the avuncular comparisons of interest (i.e. those capable of distinguishing familial confound from environmental effect) relied on only a small proportion of the samples used and as such were seriously underpowered. Some of the early MZ difference CoT studies of schizophrenia incorporated the recruitment of discordant twin pairs into their study design (Fischer, 1971; Gottesman & Bertelsen, 1989), and this is perhaps an approach that could benefit other CoT studies concerned with the intergenerational transmission of highly heritable dichotomous disorders.

A Systematic Review of CoT Studies

We used the Web of Knowledge Database to conduct our systematic review. Initially we searched for articles containing the phrase “children of twins” or “offspring of twins”. This resulted in 81 articles being identified. Of these 15 were not relevant, 4 were reviews that mentioned the CoT design (Agrawal & Lynskey, 2008; Button, Maughan, & McGuffin, 2007; D’Onofrio et al., 2013; Heath & Nelson, 2002), and 1 was an editorial piece (D’Onofrio, 2009). Of the remaining 61 results, 5 were methodological papers discussing extended twin models and/or assessing their assumptions (Eaves, Silberg, & Maes, 2005; Koenig, Jacob, Haber & Xian, 2010; Maes et al., 2009; Medland & Keller, 2009; Silberg & Eaves, 2004) and the 56 remaining results pertained to empirical studies employing the CoT method - 42 research articles and 14 conference abstracts. All of the conference abstracts could be identified as earlier versions of articles included in the search results and were thus excluded. Of the 42 research articles we identified we did not include 4 in the final review because they did not focus on phenotypes that are psychological/behavioral: Two focussed on gestational age and birth weight (Clausson, Lichtenstein & Cnattingius, 2000; York et al., 2013 – an offspring of twins and siblings study), one focussed on BMI fluctuation (Bergin et al., 2012); and another was concerned with oral cleft (Grosen et al., 2010).

To ensure that we identified all relevant articles we also conducted a far broader search for articles containing the words “children” AND “twins” in the topic. We refined this search to include

only those results included in the following Web of Science subcategories: Psychiatry; Psychology Developmental; Psychology; Psychology Multidisciplinary; Clinical Neurology; Neurosciences; Behavioral Sciences; Psychology Clinical; Psychology Educational; Psychology Experimental; Psychology Social; Substance Abuse; Social Sciences Biomedical; Psychology Biological; Social Sciences Interdisciplinary; Sociology; Social Work; Psychology Psychoanalysis; Social Issues; Social Sciences Mathematical; Psychology Applied. This resulted in 2,050 articles. We then checked the titles and abstracts of these articles. Where CoT were mentioned we checked the article contents and included all of those empirical articles that used a sample of twins and their children to examine the association between parental phenotype and child phenotype. In this manner we identified no more papers relevant to this review.

We also used mailing lists to contact researchers and asked them to inform us of any CoT articles that we may have missed in our search of the literature or that they or their colleagues had submitted for review/were in press. This resulted in 12 more articles being brought to our attention. We include 5 of these in our review. Of the 7 we do not include, 5 are CoT studies that focus on phenotypes that are not psychological/behavioral: 2 focus on birth weight (Magnus, Berg, & Bjerkedal, 1985; Nance, Kramer, Corey, Winter, & Eaves, 1983), 2 examine whether increased schooling in one generation has a knock on effect on the schooling of the next (Behrman & Rosenzweig, 2002; Bingley, Christensen & Jensen, 2009) and 1 examined the intergenerational transmission of income (Amin, Lundborg & Rooth, 2011). One study was concerned with fecundity in twins (Nisen et al., 2013). Another used a CoT sample but was not designed to make use of avuncular correlations to distinguish rGE from environmental effect (Agrawal et al., 2010).

In total we have identified 43 CoT articles concerned with distinguishing genetic from environmental transmission in the association between parental phenotype and offspring phenotype. Thirty-six of these are displayed in Table 3. Of the 7 articles not included in Table 3, 5 of them (Scherrer et al., 2012a; Scherrer et al., 2012b; Sartor et al. 2008; Sartor et al. 2010; Xian et al. 2010) are concerned with predictors of smoking behaviors and, while the primary research question

of each is distinct, they all include the same CoT data/analyses – that was first included in Volk et al. (2007). Similarly 2 articles concerned with drug dependence (Scherrer et al., 2008a; 2008b) repeat analyses included in Duncan et al. (2008). Results are arranged in alphabetical order of first author. We include details on samples, measures and control variables used in the study. We also highlight whether or not genetic and/or environmental transmission was detected, and what form (if any) of rGE was detected. In interpreting the rGE column it should be noted that most CoT studies are not set up to distinguish forms of rGE. Occasionally the design of the study or the question asked will indicate that rGE could only be of one form but often this is not the case. Only some ECoT studies are designed to distinguish passive from evocative rGE (Narusyte et al., 2008). As such the rGE column only specifies the form of rGE identified where the research design allows for such distinctions to be made.

Below we order our discussion of the CoT literature thematically as follows: First we focus on those papers concerned with the intergenerational transmission of emotional and behavioral disorders from parent to child; second, we look at the impact of parenting style on child outcome; third we examine papers concerned with the impact of the family environment (i.e. marital instability, family climate) on child outcome. We then briefly discuss alternative uses for CoT samples before moving onto a broader discussion in which we collate findings and draw out overarching themes. We finish with a discussion on the future of the CoT method.

>>Insert Table 3 around here

Intergenerational Transmission of Emotional and Behavioral Disorders

Parental Psychoses

The first CoT studies were designed to assess why psychotic disorders such as schizophrenia run in families – whether being reared by a schizophrenic parent is itself a risk factor for psychosis or whether intergenerational transmission can be explained by shared familial factors. In the first of

these studies Fischer, (1971) examined the prevalence of psychoses in the offspring of monozygotic twins discordant for schizophrenia diagnosis. Analyses revealed that rates of diagnoses in the offspring of twins diagnosed with schizophrenia were not significantly different to the offspring of those who were not diagnosed, indicating that the intergenerational transmission of psychosis is familial in nature and not the result of being exposed to a schizophrenic parent. That is, exposure to a schizophrenic parent conferred no additional risk beyond that attributable to familial confounding. Almost two decades later the twins included in Fischer's (1971) paper were followed up (this time dizygotic twins were included in analyses as well) and they and their children reassessed (Gottesman & Bertelsen, 1989). By this time all of the twins and most of their offspring had passed through the risk period for the development of schizophrenia. Results reaffirmed the conclusions contained in the first paper – again demonstrating that the intergenerational transmission of schizophrenia is familial in nature. These findings were also replicated in a separate sample of MZ twin families using structured interviews to assess rates of schizophrenia (as opposed to the clinical diagnoses used in the above studies) (Kringlen, 1987).

Parental Depression

Although CoT studies suggest that the intergenerational transmission of psychosis can be attributed to shared familial factors, CoT studies investigating other forms of psychopathology demonstrate that the emotions and behavior of parents can and do impact upon the wellbeing of their offspring above and beyond familial confounds. Depression is a common form of psychopathology and, given that depression does not appear to negatively impact upon fecundity (Power et al. 2012), many children are likely to be exposed to a depressed parent while growing up. To date two CoT articles have examined the association between parental depression and offspring depression (Silberg et al., 2010; Singh, et al., 2011). The first study (Silberg et al., 2010) involved applying SEMs (of the kind shown in Figure 3) to the combined Mid-Atlantic Twin Registry (MATR), a representative US sample of twins with children aged 9-17 years old (Anderson, Beverly, Corey, & Murrelle, 2002 2002), and

the Virginia Twin Study of Adolescent Behavioral Development (VTSABD), a US sample of adolescent twins and their parents (Hewitt et al., 1997; Eaves et al., 1997). The results of model fitting indicated that the relationship between parental depression and child depression was not significantly inflated by genetic or environmental confounds. That is, it was possible to drop genetic transmission from the model without significantly affecting model fit. The second study (Singh et al., 2011) used the Australian Twin Registry (ATR) (Hopper et al; 2006). Results were similar, again suggesting that the association between depression in parents and children was environmental and was not confounded by rGE. This suggests that estimates of the phenotypic effect of parental depression on child depression obtained in epidemiological samples are probably not substantially inflated by familial confounds. However, this lack of genetic overlap is perhaps contrary to what one might expect given that depression is a heritable phenotype. That is, if depression is approximately 40% heritable (Sullivan, Neale, & Kendler, 2000) then surely genes should play a role in its intergenerational transmission? The finding that genes do not play such a role may be the result of assessing depression during different life stages in the parent and offspring generations. In both studies 'adult' depression was compared to 'adolescent' depression. Depression is less heritable in children and adolescents than it is in adults (Rice, Harold & Thapar, 2002; Thapar & Rice, 2006), and evidence from longitudinal twin studies suggests that genetic factors involved in depression change across the lifespan (Kendler, Gardner & Lichtenstein, 2008; Lau & Eley, 2006), indicating that although a child may inherit genetic factors associated with depression from their mother it is entirely possible that simultaneously occurring child and mother depression will not share genetic commonalities. In other words, continuity in depression from childhood to adulthood may not be genetically mediated. It is possible that assessing parent and offspring depression during the same time period (i.e. under the age of 18) would reveal genetic overlap.

As well as predicting depression in the offspring generation, parental depression has also been linked to other forms of psychopathology in offspring. Silberg et al. (2010) and Singh et al. (2011) investigated whether parental depression predicted offspring conduct problems. Intriguingly, while

the parent-depression/offspring-depression association was not affected by shared genes, both Silberg et al. (2010) and Singh et al. (2011) report that the link between parent depression and offspring conduct problems was confounded by genetic overlap. That is, genetic factors associated with depression in the parent generation were associated with conduct problems in the offspring generation. Evidence for an environmental effect of parental depression on child conduct problems was equivocal: Silberg et al. (2010) report that after accounting for genetic overlap there was still a phenotypic effect of parental depression on child conduct problems. However, (Singh et al., 2011) report that once genetic overlap was accounted for, no significant association remained. The contrasting nature of the relationship that parental depression has with offspring depression and offspring antisocial behavior is curious. Phenotypic relationships between parental depression and offspring depression/antisocial behavior were similar, so differences in findings cannot be ascribed to power issues relating to decomposing intergenerational correlations of differing magnitudes. Findings await replication but at present suggest that depression in adulthood shares more genetic variance with adolescent *conduct* disorder than with adolescent *depression*. This may suggest that child conduct problems represent an early indicator of genetic risk for adult depression. The environmental association between parent and child depression suggests that exposure to a depressed parent is a risk factor for child/adolescent depression even though different genes may be involved in child and adult depression.

Perceived self-competence has been suggested as a mediatory mechanism in the link between parent depression and offspring depression, whereby parent depression leads to low-levels of perceived self-competence in offspring, which then manifests as depression (Jacquez, Cole, & Searle, 2004). Class et al. (2012) conducted CoT analyses of this association in the Twin and Offspring Study of Sweden (TOSS), a study of Swedish twins and their adolescent offspring (Neiderhiser & Lichtenstein, 2008). Analyses revealed sex differences in the nature of transmission such that associations between maternal depressive symptoms and offspring perceived self-competence were not significant once shared genetic/environmental liability was controlled for. However, the

association between paternal depression and offspring self-competence was independent of such confounds. This is the only CoT study to examine sex differences in the nature of transmission between parental depression and offspring outcome and demonstrates that mothers and fathers can impact on their child's well being in different ways.

Parental Antisocial Behavior

Similar to depression, antisocial behavior is a common form of psychopathology and antisocial behavior in parents is often associated with negative outcomes in offspring so it is important that attempts are made to understand the impact that antisocial parents may have on the development of their children. To date two CoT studies have examined the impact of parental antisocial behavior on child outcomes (D'Onofrio et al., 2006; Silberg, Maes, & Eaves, 2012). The first (D'Onofrio, Slutske et al., 2007) used HLM to examine the phenomenon of child conduct problems running in families in the ATR. Results showed that the nature of intergenerational transmission was different for boys and girls. In girls there was no environmental effect of parent conduct problems on offspring conduct problems – the association was purely genetic. However, in boys there was evidence for an environmental effect even after genetic transmission was accounted for. That is, parents who had exhibited conduct problems in their youth passed on the genetic tendency towards such behavior to both their sons *and* their daughters but provided a rearing environment that was further conducive to the development of conduct problems in boys only. Because this study focussed on child conduct problems in both generations any association remaining after accounting for genetic confounds is necessarily indirect – for example, via the adult antisocial behavior or parenting style of the parent. However, Silberg et al. (2012) used SEMs to examine the effects of antisocial personality in the parent generation on concurrent child conduct disturbance in the combined MATR/VTSABD sample. Similar to D'Onofrio et al. (2007), analyses suggested that the link between parental antisocial behavior and child conduct disturbance involved both genetic and environmental transmission – it was not possible to drop genetic or environmental pathways from the model. Silberg et al. (2012)

did not however report sex differences so it is unclear whether patterns were the same or different for boys and girls. Together, the studies of Silberg et al. (2012) and D'Onofrio et al. (2007) indicate that the effect of parental antisocial behavior on child antisocial behavior is partially confounded by genetic correlation. As such, studies of parent-child transmission of antisocial behavior that do not account for genetic confounds are likely overestimating associations. However, even after controlling for rGE there does remain an environmental effect, although this environmental effect may not be present in girls (D'Onofrio et al., 2007).

It is interesting to note that antisocial behavior in parents and their children shows genetic overlap (Silberg et al., 2012) whereas depression in parents and their children does not (Silberg et al., 2010; Singh et al., 2011). Extrapolating, this may suggest that there is greater stability in the genetic factors involved in antisocial behavior across the lifespan than in those involved in depression across the lifespan.

Silberg et al. (2012) also created two further SEMs to examine the relationships that parental antisocial behavior has with child depression and hyperactivity. In the child hyperactivity model the association between parent antisocial behavior and child hyperactivity was entirely genetic – the environmental pathway was not significant. This finding lends support to the generalist genes hypothesis – the notion that many of the same genes underlie distinct psychiatric disorders and this genetic overlap largely accounts for the co-occurrence of disorders (Andrews et al., 2009; Eley, 1997; Kovas & Plomin, 2006; Kreuger et al., 2002). In this case genetic overlap appears to account for the cross-disorder intergenerational transmission of psychiatric disorders. That is, genes related to antisocial behavior in the parent generation were passed on to the next generation in whom those genes were involved in the hyperactivity. In combination with the evidence demonstrating the genetic transmission of conduct problems, these findings further demonstrate the important role that genes play in the intergenerational transmission of externalizing behaviors. In contrast, in the child depression model there was no significant genetic association between parental antisocial

behavior and child depression. Instead the association appeared to be environmental. That is, being reared by an antisocial parent was an environmental risk factor for the development of child depression. This observation contrasts with the reverse relationship, where the link between parental depression and child antisocial behavior was found to be genetic (Silberg et al. 2010, Singh et al. 2011). This would suggest that although adult depression and child antisocial behavior share genetic overlap, adult antisocial behavior and child depression do not. Coupled with the finding that the link between child depression and parent depression is also environmental and not genetic (Silberg et al. 2010, Singh et al. 2011), the environmental link between parent antisocial behavior and child depression suggests that child depression may largely be a response to a negative rearing environment, with genetic factors playing a lesser role. This is a finding that coincides with reports that depression is less heritable in childhood than in later life (Rice, Harold & Thapar, 2002; Thapar & Rice, 2006), and is often linked with a poor quality rearing environment (Birmaher et al. 1996).

In summary CoT studies of the intergenerational transmission of emotional and behavioral problems seem to have revealed some interesting patterns. First, the transmission of psychosis from one generation to the next appears to be familial with no evidence for a significant effect of being reared by a parent with psychosis. Second, parental depression appears to have a direct environmental effect on child depression not confounded by genetic overlap and an effect on child antisocial behavior that is partially confounded by common genes. Third, the associations that parental antisocial behavior have with child antisocial behavior and hyperactivity is confounded by genetic overlap. Accounting for that overlap leaves an environmental association with antisocial behavior only. Parental antisocial behavior also has a direct effect on child depression not confounded by shared genes.

Parental Alcoholism

Parental alcoholism is a well-known risk factor for a host of negative outcomes and this perhaps explains why it is the parental phenotype most often examined in CoT studies. To date 9 CoT studies

have looked at the effects of parental alcohol problems on child outcome (Duncan et al., 2006; Glowinski et al., 2004; Haber, Jacob, & Heath, 2005; Jacob et al., 2003; Knopik et al., 2006; Knopik, Jacob, Haber, Swenson, & Howell, 2009; Slutske et al., 2008; Waldron, Martin, & Heath, 2009). Two CoT samples appear to have been comprised with the study of alcoholism in mind. The first, taken from the ATR, comprises several waves of data collection, one of which included a psychiatric interview (Hopper et al., 2006). Half of the sample was selected so that at least one twin reported a history of alcohol dependence, conduct disorder, depression or divorce. The other half of the sample comprised randomly selected twin pairs not at risk for psychopathology. As such the CoT ATR sample is an at-risk group. The second CoT sample used for the investigation of substance use was taken from the Vietnam Era Twin Registry (VETR), a sample composed of male-male twin pairs who served in the US military between 1965 and 1975 (Goldberg, Curran, Vitek, Henderson, & Boyko, 2002). All of the 9 CoT studies examining parental alcoholism use one of these two samples. All of these articles employed HLMs to analyse data.

Three CoT studies have examined the transmission of alcohol problems from one generation to the next (Duncan et al., 2006; Jacob et al., 2003; Slutske et al., 2008). The first (Jacob et al., 2003) used the VETR sample to examine the effects of paternal alcoholism on offspring alcoholism. Because the VETR is an at-risk sample analyses included controls for a range of psychiatric disorders in twins. Spousal alcoholism, psychiatric problems and use of substances during pregnancy were also controlled for. Although there was a clear association between paternal alcoholism and offspring alcoholism, there was limited evidence to support either a genetic or environmental link between paternal alcoholism and offspring alcoholism. Those at high genetic and high environmental risk (i.e. those with an alcoholic father) were more likely than other groups to display alcohol problems themselves, however it was not possible to distinguish genetic from environmental effects. Point estimates did indicate that individuals whose father was not alcoholic but who had an alcoholic MZ co-twin (high genetic, low environmental risk) were less likely to be alcoholic themselves than were those whose father was alcoholic (high genetic, high environmental risk). Such an observation is

suggestive of an environmental effect of paternal alcoholism but analyses did not identify significant differences in risk for alcoholism in these groups – an observation itself indicative of genetic effects. There were also limitations to this study: Offspring ranged in age from 12 to 26 years so many had still not gone through the adolescence/early adulthood phase, during which risk for alcohol problems peaks. The age at which offspring were exposed to parental alcoholism was also not taken into consideration. Thus, (Duncan et al., 2006) effectively repeated this study some years later, with the independent variable being updated to identify offspring exposure to paternal alcoholism during their 'formative' years (prior to age 12) as opposed to ever. However, results again did not provide any compelling evidence for an effect of parental alcoholism on offspring alcoholism once familial confounds were accounted for. These 2 studies focussed on paternal alcoholism only, and included offspring too young to legally drink. However, Slutske et al. (2008) examined the effects of paternal *and* maternal alcoholism (a continuous measure of alcohol use disorder symptoms) on offspring alcoholism in the ATR dataset, focussing only on offspring over the legal age of alcohol consumption. Again, controls were included to account for psychopathology in the twins as in the VETR studies. Analyses were somewhat underpowered, with overlapping confidence intervals making it difficult to draw firm conclusions. However, point estimates indicated that once familial confounds were accounted for, the effect of parental alcoholism on offspring alcoholism was likely modest at best, and in this study was not significant.

In summary, of the 3 CoT studies that have examined the transmission of alcoholism from one generation to the next, none have found evidence for a significant environmental effect of parental alcoholism. However, before dismissing the impact of parental alcoholism on offspring alcoholism, Jacob et al., (2003) highlight one finding of importance in understanding the development of alcohol problems. They note that the offspring of unaffected MZ twins whose co-twin was alcohol dependent (i.e. those at genetic risk but raised in a no-risk environment) were no more likely than offspring of non-alcoholic twins with unaffected co-twins (no genetic risk and no environmental risk) to develop alcohol problems themselves. This was also the case in Duncan et al.'s (2006) analysis and

Slutske et al.'s (2008) paper. This suggests that genetic risk for alcoholism can be tempered – that genetic risk alone is not enough to develop alcohol problems. That is, an environment conducive to the development of alcoholism (in the form of an alcoholic parent) is also needed. Jacob et al. (2003) point out that this is suggestive of a gene-environment interaction.

Other CoT studies have assessed the impact of parental alcohol problems on the development of other forms of offspring psychopathology. Two such studies have examined the relationship between parental alcoholism and ADHD problems (Knopik et al., 2006; Knopik et al., 2009). The first examined the effects of maternal alcohol use disorder on offspring ADHD in the ATR sample (Knopik et al., 2006). Results demonstrated that offspring of non-alcoholic mothers with an alcoholic MZ twin were at increased risk of ADHD relative to controls (unaffected parent with unaffected twin) but did not differ in their risk compared to offspring of unaffected mothers with an affected DZ twin. Thus, the results offer support for genetic transmission. There was no difference in risk for ADHD between offspring of alcoholic parents and offspring of non-alcoholic parents with an alcoholic MZ twin, thus there was no evidence for an environmental effect. The second such study was conducted on the VETR sample and focussed on the effects of paternal alcoholism on offspring attention-deficit-hyperactivity-problems (Knopik et al., 2009). Again parental psychopathology and substance use were controlled for. Results followed the same pattern as those of Knopik et al., (2006) in providing no support for the notion that paternal alcoholism had a direct environmental effect on offspring ADHD but providing some evidence for genetic transmission.

Two CoT studies have examined the relationship between parental alcoholism and conduct problems (Haber et al., 2005; Waldron et al., 2009). The first used the VETR to investigate the relationship between paternal alcoholism and offspring conduct disorder symptoms (Haber et al., 2005). Analyses revealed that after controlling for familial confounds there was no evidence of an environmental effect of paternal alcoholism. Results were suggestive of a genetic link, although statistical significance was not achieved. The second such study used the ATR to examine the

association between parental alcohol use disorder and offspring externalizing problems (Waldron et al., 2009). Results indicated that the association was genetic in nature – those at no environmental risk but heightened genetic risk (offspring of -alcoholic parents with alcoholic MZ twins) had greater externalizing problems than those at no environmental risk and moderate genetic risk (offspring of -alcoholic parents with alcoholic DZ twins). There was no support for environmental transmission – the risk was equivalent for offspring of alcoholic parents and offspring of non-alcoholic parents with alcoholic MZ twins.

As well as examining the relationship between parental alcoholism and externalizing, Waldron et al. (2009) also looked at the impact of parental alcoholism and internalizing problems. No evidence was found to support the notion of an environmental effect. Although point estimates suggested genetic transmission may have been involved, the relevant comparisons were not significant. One other study looked at the association between paternal alcohol dependence and offspring suicidal behaviors in the VET sample (Glowinski et al., 2004). Analyses suggested that both genetic and environmental transmission may have been operating. However after controlling for covariates the phenotypic association between paternal alcoholism and offspring suicidal behaviors was not significant, so no clear conclusions could be drawn.

In summary, CoT studies that have examined the impact of parental alcoholism have failed to detect a significant environmental influence of parental alcoholism on offspring alcohol problems (Duncan et al., 2006; Jacob et al., 2003; Slutske et al., 2008), offspring ADHD (Knopik et al., 2006; Knopik et al., 2009), externalizing problems (Haber et al., 2005; Waldron et al., 2005), or internalizing problems (Glowinski et al., 2004; Waldron et al., 2009). Most studies found that phenotypic associations between parental alcoholism and offspring psychopathology were likely genetic in nature (or at least that no significant environmental effect remained once familial confounds were accounted for). These findings should however be interpreted within the context of some limitations (limitations originally noted by the authors of the articles themselves). First, these findings all stem from two

studies – the ATR and the VETR. Both of these studies used psychiatric diagnoses as the primary measure of psychopathology. In both cases the measures used appear to be of a very high quality for such large studies, involving in-depth interviews with participants. Although the use of such high quality measures has obvious advantages, the use of dichotomous variables reduces statistical power to identify significant differences between relationships. In the above studies this has led to an inability in many cases to state within statistically acceptable levels of certainty whether relationships were genetic or environmental in nature. Slutske et al. (2008) as well as others before them (Schmidt, 1996) highlight that it is important in such cases to report confidence intervals, and to interpret point estimates (i.e. odds ratios or beta coefficients) as indicative of the likely direction of effects where confidence intervals suggest that, given greater power, such interpretations would likely be correct. Indeed, we have tried to do this in reviewing these articles, both within the text and in Table 3. Broadly speaking, most of the CoT studies of parental alcoholism support the hypothesis that intergenerational links between parental alcoholism and offspring psychopathology are likely genetic in nature with limited support for an environmental effect. However, such interpretations are open to criticism and await replication. We appreciate that there is an ongoing debate regarding the dimensional or categorical nature of psychopathology (Coghill & Sonuga-Barke, 2012), however for purely practical reasons future CoT studies of parental alcoholism would do well to adopt continuous measures of alcoholism and offspring psychopathology.

Another limitation is that the measures used in the studies reviewed may have done a better job of capturing genetic risk than they did of capturing environmental risk. That is, if a child's parent has at some point in their life been diagnosed with alcohol dependency then it is appropriate to label that child as being at heightened genetic risk for alcohol dependency. However, a richer measure is likely needed to capture whether and to what extent the child is exposed to that alcoholism as an environmental risk. That is, an alcoholic parent may or may not drink or get intoxicated in the presence of their children. They may or may not have been alcohol dependent when the child was developmentally sensitive to such an environmental risk (or even, given the broad age range of

participants in the 2 samples used, when the child was living at home). Duncan et al. (2006) did attempt to address this but their age range of sensitivity (birth to 12 years old) appears to have been defined more by the data available than by any empirically derived hypothesis. Indeed it is conceivable that adolescence could also constitute a developmentally susceptible period to the negative effects of parental alcoholism. For example, substance use is known to impact parenting (Schuler, Nair & Black, 2002), and given the role of parenting in curtailing involvement in antisocial behavior and substance use during adolescence (Dishion & McMahon, 1998), it seems likely that adolescence could be a period when exposure to a substance abusing parent would also have negative consequences. Future CoT studies of parental alcoholism would therefore benefit from incorporating measures that assess the child's degree of exposure to paternal alcohol abuse, the timing of that exposure (i.e. infancy, childhood, adolescence), as well as parenting measures that may moderate the effects of parental substance use on offspring outcomes.

Despite the limitations discussed the studies reviewed in this section have many strengths, such as the inclusion of a large number of control variables, the high quality of measures used, and the use of at-risk datasets. As such the broad finding that unites these studies –that the relationship between parental alcoholism and offspring psychopathology is inflated by familial confounds– may well prove reliable.

Parental Drug Use/Abuse

Drug use and abuse in parents is a well established risk factor for the development of a host of negative outcomes in children. It is easy to imagine that drug abuse could damage a parent's ability to care for their children, result in poor parenting practices, and potentially lead to neglect and abuse. However, substance abuse is heritable (Hopfer, Crowley, & Hewitt, 2003) and the association between parental substance use and negative child outcomes could be the product of rGE and/or a range of associated confounds. CoT studies are one way in which researchers can elucidate the nature of associations between substance abuse and child psychopathology.

Three studies have used the VETR sample to investigate predictors of offspring cannabis abuse and dependence while controlling for genetic confounds related to parental drug dependence (Duncan et al., 2008; Scherrer et al., 2008; 2009; included in Table 3 as a single entry). While the primary hypotheses of these studies related to the effects of childhood physical/sexual abuse (Duncan et al., 2008), sibling and peer substance use (Scherrer et al., 2008), and the subjective effects of cannabis use (Scherrer et al., 2009) as predictors of cannabis abuse and dependence, we focus here on what these studies can tell us about intergenerational transmission. That is, whether the relationship between parental drug dependence and offspring cannabis abuse/dependence is genetic and/or environmental in nature. Results revealed that offspring at high genetic and high environmental risk (those whose father reported drug dependence) were at greater risk of developing cannabis abuse/dependence than were those in other risk groups but it was not possible to distinguish between genetic and environmental factors. This could indicate that the combination of genetic factors and an environment conducive to drug use are both necessary for the development of cannabis abuse/dependence. However, one limitation to this study was the small number of offspring who were at genetic risk but were not at environmental risk (i.e. those with a substance using uncle but without a substance using father). This means that the study had limited power to distinguish genetic from environmental transmission because very few offspring were subject to only one source of risk.

The only CoT study to show an environmental effect of parental substance use is that of Haber et al. (2010). Using the VETR sample they demonstrated that the association between drug dependence in male twin pairs and conduct disorder in their offspring was both genetic and environmental in nature. Although there was a genetic confound drug dependence in fathers still predicted elevated conduct problems in offspring after genetic risk was accounted for. Haber et al. (2010) contrasted this analysis with one that again showed that there was no detectable environmental effect of parental alcohol dependence on offspring conduct disorder.

Haber et al.'s (2010) study appears to be the only CoT study to demonstrate an environmental effect of parental substance use on offspring adjustment. Using data from the ATR McCutcheon et al. (2013) examined the nature of comorbidity in the offspring of substance using twin fathers. They identified four latent classes that could describe the clustering of disorders in offspring: unaffected, alcohol use/disorder, alcohol use-depression-anxiety, and substance use-conduct problems. Although it was clear that substance use in the parent generation was associated with these negative outcomes in the offspring generation, the study was not able to distinguish between genetic and environmental transmission. In summary, the evidence for an effect of parental substance use on child adjustment is limited. It is probable that these studies also suffer from the same drawbacks as those discussed above in relation to parental alcoholism. Namely, that the use of lifetime psychiatric diagnoses as a predictor results in low power and poorly defined environmental risk.

Smoking

Parental smoking has long been highlighted as detrimental to the health and wellbeing of children, especially during the prenatal and childhood phases of development. For example, smoking during pregnancy has long been associated with low birth weight in offspring and while tobacco companies have cast doubt on causal links between smoking and negative health outcomes, 2 CoT studies have been able to demonstrate that this effect is still significant once genetic confounds are taken into account (D'Onofrio et al., 2003; Magnus, Berg, Bjerkedal & Nance, 1985). In one of the earliest CoT twin studies to include both MZ and DZ twins, Magnus et al. (1985) using a small sample of Norwegian twins, showed that mothers that smoked during pregnancy gave birth to smaller children than did their co-twin. D'Onofrio et al. (2003) combined data from the Virginia Twin Registry and the Norwegian Twin Panel and, through the use of SEM, showed that although the tendency to smoke during pregnancy was under genetic influence, these genes were not associated with offspring birth

weight, and the effect of exposure to maternal smoking during pregnancy was not accounted for by familial confounds.

Smoking is itself heritable and smoking behaviors tend to run in families. Volk et al. (2007) used the VETR sample to investigate whether the correlation between father and offspring nicotine dependence could best be explained as genetic transmission or whether having a nicotine dependent father acted as an environmental risk factor for nicotine dependence in offspring. Results suggested that some of the association was genetic, but that an effect of exposure remained after controlling for familial risk. Volk et al. (2007) were also interested in the association between nicotine dependence and alcohol dependence and in particular whether the transmission of risk was specific or shared across these two correlated phenotypes. Results indicated that familial risk for nicotine dependence predicted only nicotine dependence in offspring, and not alcohol dependence. Similarly, familial risk for alcohol dependence predicted offspring alcohol dependence but not nicotine dependence. Thus, although these two phenotypes are known to share aetiologies when measured in a single generation, when assessed across two generations risk appears to be specific.

The Effects of Parenting on Child Outcome

CoT studies that have focussed on the transmission of disorder from parent to child can tell us a lot about whether emotional or behavioral difficulties in parents have an effect on their children's well being. However, where environmental effects are detected these studies typically tell us very little about the likely mechanisms through which parental problems lead to child problems. For example, why are children raised by a depressed parent more likely than others to develop depression?

Modelling of parental behavior may play a role but similarly the parent-child relationship (Overbeek, Stattin, Vermhulst, Ha & Engels, 2007), parenting behavior (Elgar, Mills, McGrath, Waschbusch & Brownridge, 2007) and interpersonal stress (Barker, 2013) are all related to parental depression and child well-being, so the impact of parental depression on child well being may operate via any number of these pathways. CoT studies can be used to examine the relationship between parenting

behavior (the behavior of the parent directed towards the child) and child outcome while accounting for familial confounds. To date 4 CoT studies have done this (Lynch et al., 2006; Marceau et al., 2013; Narusyte et al., 2008; Narusyte et al., 2011). The first examined the relationship between harsh punishment and offspring behavioral problems in the ATR dataset (Lynch et al., 2006). Numerous studies have linked harsh punishment with negative outcomes in children (Gershoff, 2002), yet without the use of a genetically informative design such as the CoT method it is not possible to distinguish effects from confounds. That is, parents who are predisposed to harsh punishment may also tend to have children predisposed to psychopathology – both phenotypes may share a common etiology. Lynch et al. (2006) made distinctions between non-physical punishment /physical punishment and mild/ harsh punishment. Child outcome measures were drug and alcohol use, externalizing problems and internalizing problems. Results of HLM suggested that harsh physical punishment was predictive of all child outcomes after controlling for confounds, but mild and non-physical punishment were not. Thus, extreme physical punishment does have an impact on the emotional wellbeing of children, whereas it does not appear that less extreme, more normative forms of punishment do so.

Three studies have examined the impact of parenting on child outcomes using the ECoT approach. As described previously, the ECoT method involves combining a children-of-twins dataset with a children-as-twins dataset and allows for the assessment of bidirectional effects between parent and child phenotype. In other words it allows researchers to examine to what extent children ‘cause’ the behavior of their parent, as well as vice versa. As such the application of ECoT models also allow for the distinction between passive rGE and active/evocative rGE.

The first ECoT study ever conducted combined the data from the TOSS dataset and the Twin Study of Child and Adolescent Development (TCHAD), a Swedish sample of adolescent twins (Lichtenstein, Tuvblad, Larsson, & Carlstrom, 2007). In this study Narusyte et al. (2008) examined the association between maternal emotional over involvement and offspring internalizing problems (Narusyte et al.,

2008). Emotional over involvement refers to overprotective, self-sacrificing parent behavior targeted towards a child and could feasibly cause or result from internalizing problems in the child. Results of SEM (using the model described in Figure 3) suggested that the relationship could best be described as evocative rGE. That is, maternal emotional over involvement and internalizing problems shared common genes but the direction of effects was such that the child's internalizing problems evoked emotional over involvement on the part of the mother. Narusyte et al.'s (2008) finding demonstrates how important it can be to consider bi-directionality when examining parent-child relationships. Other ECoT findings confirm this. For example, in a second study using the same samples Narusyte et al. (2011) report that the relationship between maternal criticism (of the child) and offspring externalizing problems can also be described as an evocative rGE. In contrast, the relationship between *paternal* criticism and externalizing problems comprised a direct parent-to-child phenotypic effect not confounded by genetic overlap. In other words a father's criticism acts as a (potentially causal) risk factor for child externalizing problems, whereas a mother's criticism is a response to the child's behavior, with maternal criticism and child externalizing also sharing common genetic factors.

Marceau et al. (2013) showed that the relationship between negative parenting (parenting involving conflict, coercion and punitive punishment) and externalizing behavior in children was also a child-to-parent effect. Because externalizing behavior was under genetic influence this relationship can be interpreted as evocative rGE. However, this particular relationship was not confounded by genetic overlap between the two constructs. That is, the genetically influenced externalizing behavior of the child evoked negative parenting (an evocative rGE), but because different genetic factors were involved in each phenotype the relationship between them was not confounded.

In summary, CoT and ECoT studies that have examined relationships between parenting style and child outcome have revealed a range of effects. Harsh physical punishment had a direct effect on child problems after controlling for familial confounds (although this was not true for mild or non-

physical punishment; Lynch et al., 2006). Similarly paternal criticism had a direct effect on child externalizing (Narusyte et al., 2011). However the relationships between child externalizing and maternal over involvement (Narusyte et al., 2008), and maternal criticism (Narusyte et al., 2011) were the product of evocative rGE – the genetically influenced behavior of the child evoking a response from their parent. The relationship between negative parenting and child externalizing was also evocative but the genes involved in negative parenting did not overlap with those involved in externalizing (Marceau et al., 2013). As such ECoT studies suggest several things: First, that relationships between parenting and child outcome vary by phenotype, there is not a single explanation that fits all parenting-child outcome relationships. Second, child behavior can play an important role in evoking parenting behavior – the parent-child relationship is demonstrably bidirectional. Third, parenting-child relationships may differ for mothers and fathers (Narusyte et al., 2011).

The Effects of the Family Environment on Child Wellbeing

Aside from the behavioral characteristics of parents, and the parenting style that they adopt with their children, the composition of, and the emotional climate within the family can have an important impact upon child and adolescent development. For example, teenage motherhood (Jaffee, Caspi, Moffitt, Belsky, & Silva, 2001; Moffitt, 2002), marital breakup (Storksen, Roysamb, Moum, & Tambs, 2005), and family structure (Bramlett & Blumberg, 2007) have all been linked to emotional well being and problem behavior in children. Indeed, the World Health Organization urges member states to reduce teenage pregnancy rates (World Health Organization, 2012), and in many countries governments endorse policies that incentivise families to stay together rather than separate (Jaffee, Moffitt, Caspi, & Taylor, 2003). However, without accounting for rGE it is impossible to tell whether the effects observed may be causal, and thus whether such policies are justified.

Adolescent motherhood has been linked with a range of adverse outcomes in offspring during childhood and beyond (Jaffee et al., 2001). Understanding the nature of the relationship between adolescent motherhood and negative child outcomes is important if policy makers are to know how to approach this issue. For example, is it that adolescent mothers are less able to provide an optimal environment for their child to develop, or do adolescent motherhood and behavioral problems share common causes? If the former is true then reducing the rate of teen pregnancies will lead to a reduction in behavioral problems. If the latter is true then identifying and addressing the common cause will lead to a reduction in both teen pregnancies and behavioral problems. Two CoT studies have investigated the association between adolescent motherhood and offspring mental health problems (Harden, et al., 2007a). In the first of these studies the relationship between adolescent motherhood and substance use, externalizing and internalizing problems in the adult offspring was assessed (Harden, et al., 2007a). The results of HLM suggested that for all 3 outcomes the effect of being born to a teenage mother remained even after controlling for possible genetic confounding. For externalizing problems and substance use there was also (marginally significant) evidence for the presence of rGE. In another study Coyne, Langstrom, Rickert, Lichtenstein and D’Onofrio (2013) made use of the national Swedish registries to create a sample of children-of-twins and children-of-siblings with which to assess the impact of maternal age at first birth on criminal convictions in offspring. Results indicated that the effect of maternal age was not confounded by familial factors and that for each one year increase in maternal age at first birth there was a dramatic 10% reduction in the likelihood of offspring being convicted. It is worth noting here that the pathway through which teenage motherhood leads to problems in offspring is not yet clear. That is, teenage motherhood is unlikely to directly *cause* problems in offspring but probably operates via some third variable or group of variables, such as a relatively reduced income, reduced support network, or via the immaturity/inexperience of the mother making it difficult to provide optimal parenting.

Another CoT study examined the intriguing observation that girls who grow up with an unrelated adult male in the household (i.e. a stepfather) reach menarche earlier than their peers (Mendle et

al., 2006). Explanations for this observation have tended to take an evolutionary perspective. For example, Belsky, Steinberg, & Draper (1991) suggested that the presence of a stepfather/absence of a biological father during childhood is an indicator of a stressful or unstable environment – in such an environment there may be reduced resources so it makes evolutionary sense to begin mating early in order to maximise the likelihood of reproductive success. Girls in such families therefore reach menarche early. Such a theory implicitly assumes that the presence of a stepfather (or absence of the biological father) ultimately *causes* early menarche. However, it is of course possible that such an association is the result of genetic or environmental confounds. That is, mothers who have unstable relationships with the father(s) of their children may be more likely to have daughters who reach menarche early. Applying HLM to the ATR sample Mendle et al., (2006) showed exactly this. They found that having a step-uncle was as predictive of early menarche as was having a stepfather, thus indicating the presence of a familial confound. Further analyses were not able to establish whether this confound was genetic or environmental but such a finding indicates that the presence of a stepfather does not *cause* early menarche. Moreover, including maternal age at menarche in the model eliminated differences in age at menarche associated with the presence of a stepfather. This suggests that the association may be due to individuals who reach menarche early being predisposed to have unstable relationships with men. Offspring resulting from these relationships will themselves inherit the predisposition to reach menarche early.

Conflict within the family unit is another source of familial risk in the development of psychopathology in children. Schermerhorn, et al. (2011) examined the relationship between family functioning (family conflict, marital discord and marital disagreement about parenting) and child adjustment (internalizing problems and externalizing problems) in the TOSS sample. A series of SEMs revealed that all aspects of family functioning were related to the development of internalizing problems in children with no evidence of genetic confounding. This was also the case for the relationship between family conflict and externalizing problems. However, genetic overlap was detected in the relationships that marital discord and disagreement-about-parenting had with

externalizing. Marital disagreement about parenting also predicted externalizing above and beyond genetic overlap but the relationship between marital discord and externalizing appeared to be entirely explained by common genetic factors. In other words, there was no evidence for a potentially causal pathway between marital conflict and externalizing problems. This last finding is supported by Harden, Turkheimer, et al. (2007) who report that in the ATR the relationship between marital conflict and offspring conduct problems could also be entirely explained in terms of passive rGE. In other words the association could be attributed to genetic factors that contribute both to marital conflict in the parent generation and conduct problems in the offspring. It would thus appear that measures of family conflict do a good job of capturing environmental risk for the development of internalizing problems in children and to some extent externalizing problems, although relationships between family conflict and externalizing may also be (at least partially) explained by genetic confounding.

While family conflict does place children at risk for the development of psychopathology, conflict can ultimately lead to divorce – itself a major risk factor for adjustment problems in offspring. Children of divorced or separated parents tend to display elevated emotional and behavioral problems compared to their peers, with a twofold increased risk for some problems (Amato 2001; Amato & Keith, 1991). Using the CoT method researchers have been able to assess whether this association remains after accounting for familial confounds. Four such studies have been conducted to date (D’Onofrio et al., 2005; D’Onofrio et al., 2006; D’Onofrio, Turkheimer, Emery, Harden et al., 2007; D’Onofrio, Turkheimer, Emery, Maes et al., 2007). Three of these studies used the ATR dataset (D’Onofrio et al., 2005; D’Onofrio et al., 2006; D’Onofrio, Turkheimer, Emery, Harden et al., 2007) and one used data taken from the Virginia 30,000, a study of twins and their families in Virginia, USA (D’Onofrio, Turkheimer, Emery, Maes et al., 2007). In both of these samples the majority of offspring were adults. D’Onofrio et al. (2005) examined the relationship between marital instability (a lifetime history of divorce and separation) and offspring psychopathology (substance use, internalizing problems and externalizing problems) in the ATR CoT sample. Results of HLM

indicated that the association between marital instability and offspring psychopathology remained significant regardless of the number of statistical controls introduced. There was no significant evidence for genetic confounding, nor did parental psychopathology account for the relationship, thus *suggesting that marital instability may play a causal role in the development of offspring psychopathology*. Findings were similar for all forms of child psychopathology. D’Onofrio, Turkheimer, Emery, Maes et al. (2007) examined the effects of marital instability (parental divorce/separation) on offspring alcohol problems and emotional problems in the Virginia 30,000. Results partially supported those of D’Onofrio et al. (2005): HLM indicated that the association between marital instability and alcohol problems was not confounded by unmeasured genetic or environmental familial factors, suggestive of an environmental effect. In contrast, the association between marital instability and emotional problems appeared to be explained by familial confounds. It is unclear why the results of these two studies should differ in regards to emotional/internalizing problems.

In another study in the ATR sample D’Onofrio et al. (2006) investigated relationships between parental divorce/separation and a range of offspring outcomes: For associations between divorce and age at first sexual intercourse, substance use, and internalizing problems, genetic factors accounted for a portion of the relationship but did not entirely account for it – that is, after controlling for genetic confounds the effects of parental divorce were still significant. Divorce was also predictive of reduced academic performance and fewer years in education and these associations were not affected by familial confounds. That is, being brought up in a ‘broken home’ appears to negatively impact on offspring education. In contrast, the relationship between parental divorce and cohabitation in offspring (the tendency to enter into cohabitating relationships that do not result in marriage) was accounted for by familial confounds. This association was thus not causal but was the product of common etiological factors shared within a family that play a role in both parental divorce and offspring cohabitation.

Like many measures of interest to behavioral scientists, marital instability runs in families. Such an observation could arise because A) as a phenotype 'marital instability' is under genetic influence and so parents transmit (genetically) the tendency towards marital instability onto their children, and/or B) the childhood experience of parental divorce affects the child in such a way that later in life they too are more likely to get divorced. Given the negative impact that parental divorce has on offspring adjustment it is important to evaluate which of these hypotheses is true. Using the ATR dataset D'Onofrio, Turkheimer, Emery, Harden et al. (2007) reported that the relationship between marital instability in the parent generation and marital instability in the next is both genetic and environmentally influenced— children of divorced parents inherit a genetic propensity towards marital instability, but the experience of parental marital instability also has an influence on the offspring's future relationships.

Overall then CoT studies would appear to indicate that marital instability does have an environmental impact on offspring outcome, even when familial confounds are taken into account. CoT studies also indicate that this is the case with adolescent motherhood (Harden, Lynch, et al., 2007), and family conflict (Harden, Turkheimer et al. 2007; Schermerhorn et al., 2011), suggesting that 'family-level' measures such as these may do a good job of describing environmental risk factors relevant to offspring emotional well-being that are either independent of familial confounds, or that have an effect above and beyond them. However, one question that has not yet been addressed within a genetically informative framework (to our knowledge) is whether marital instability and family conflict each have an independent impact on child wellbeing or whether they confound one another. To rephrase, is it the conflict that has the lasting negative impact upon the child and/or is it the separation of their parents and the resultant distress and upheaval? If it is the conflict then divorce should not be viewed as a cause of psychopathology in offspring and should perhaps not be discouraged by governments – indeed it may do good in ending a period of conflict. In reality this issue is likely to be complex with many moderating factors but the CoT design is likely to prove to be one of the best for identifying potential causal factors.

As discussed earlier in this article, one limitation of the CoT design is that when the parental measure of interest is 'multi-agent' in nature, it can become difficult to interpret findings. That is to say, marital discord, divorce, or disagreement, are essentially dyadic in nature so the results of CoT models may be somewhat ambiguous. This is a limitation and does cast doubt on the validity of some of the CoT findings relating to marital instability. However, in defence of the CoT articles that use such measures, most adopted a 'lifetime history' measure of marital instability. Lifetime history measures of relationship difficulties likely represent something closer to a characteristic of the twin than do measures relating to a single relationship, and so the use of such measures goes some way to resolving issues of ambiguity. Furthermore, most studies also included measures of spousal characteristics as control variables.

Overview of Findings to Date

Over the past decade the CoT design has been used to elucidate the mechanisms underlying relationships between parent and child phenotypes: The transmission of psychosis from one generation to the next appears likely to be genetic in nature, whereas parental antisocial behavior and depression both appear to have a phenotypic effect on offspring wellbeing after accounting for familial confounds. To date CoT studies have revealed little support for the notion of parental substance use being an environmental risk factor for the development of offspring substance use and related psychopathology. Any associations appear to be attributable to common familial factors and/or related psychopathology. Studies of parenting practises have revealed several parenting behaviors that may provide a pathway through which psychopathology is transmitted from one generation to the next. Focussing on possible mechanisms such as parenting may give researchers a better handle on routes of transmission and inform as to how best to design interventions. Importantly ECoT studies also make it clear that children can affect their parent's behavior just as much as parents affect their children. Marital discord, family conflict, and other measures tapping

dysfunction within the family unit appear to be important predictors of offspring psychopathology even after accounting for familial confounds.

Through the identification of parent phenotypes that predict negative child outcomes, CoT projects can aid researchers in identifying which of the many documented risk factors for offspring psychopathology are indeed risk factors once familial confounding is accounted for. This of course applies to other research designs capable of accounting for such confounds, and together CoT studies, adoption studies and other genetically informative family studies can help to inform clinicians, practitioners and interventionists as to which parent behaviors to target and how.

Genetic overlap between parent and child phenotypes appears common in CoT analyses, with many studies of cross-disorder transmission (i.e. the relationship between one trait in the parent population and another in the offspring) lending support to the findings of genetic overlap within more traditional 'single generation' twin studies. There are many examples from the twin literature (Andrews et al., 2009; Krueger et al. 2002, Plomin & Kovas, 2005) demonstrating a high degree of genetic overlap between behavioral and emotional traits and disorders, indicating that the same genes are involved in a range of related phenotypes within individuals. The CoT literature confirms and extends these findings in demonstrating that genetic factors involved in one disorder in the parent generation are often associated with another disorder in the offspring generation.

CoT research has not been without problems. Some of the studies conducted have been underpowered, some of the findings are inconsistent across studies, and the methodology of some studies have been criticised by others (see Eaves et al., 2005). Many of the problems encountered by CoT researchers serve to highlight the relative immaturity of the CoT method and literature – the vast majority of studies have been published within the last decade and have utilised only a small number of datasets. As such it is sometimes difficult to draw firm conclusions regarding the nature of relationships between specific parent and child phenotypes by relying on the CoT literature alone. As is always the case each method brings with it limitations so it is also important that researchers

apply multiple genetically informative methods to issues of intergenerational transmission of psychopathology, the influence of parenting practices on child development, and the effects of the family environment on offspring wellbeing. For example, longitudinal studies of adoptees and their adoptive parents can estimate parent-to-child and child-to-parent effects independent of genetic confounding (e.g. O'Connor, Deater-Deckard, Fulker, Rutter & Plomin, 1998; O'Connor, Caspi, DeFries & Plomin, 2000; Leve et al. 2012; Leve et al., 2013). Similarly, samples involving offspring conceived using assisted reproductive technologies may include children who are genetically related to both of their parents, one parent only, or neither parent, so can also be used to estimate genetic and environmental effects in relationships between parent and child characteristics (e.g. Harold, Rice, Hay, van den Bree & Thapar 2011; Thapar et al., 2007; Thapar et al., 2009). It is also possible to evaluate the nature of intergenerational transmission in samples of non-twin parent-child dyads where the parent generation comprises full/half siblings and/or cousins. Such samples can be stratified into groups of differential genetic relatedness and comparisons between them used to infer the genetic/environmental influences on intergenerational correlations in the same way that samples of MZ and DZ twins and their children are used. The problem here is that where MZ and DZ twins share 100% and 50% of their genetic relatedness, half-siblings, cousins and half-cousins share only 25%, 12.5% and 6.25% respectively. As such these comparisons have only low power to detect genetic effects so very large samples are needed for such an approach to work. Fortunately some countries (e.g. Scandinavian countries) keep population registers that can be used by researchers interested in decomposing the effects of parent phenotype on child phenotype into genetic and environmental effects. For example, Jundong et al. (2012) linked longitudinal national population registers in Sweden to compare school performance of the offspring of schizophrenic and non-schizophrenic parents, resulting in a sample of over 1.4 million individuals. Results indicated that genetic factors accounted for the association between parental schizophrenia and poor school performance in offspring.

Alternative Uses of CoT Data

In order to keep this article focussed in its aims we constrained our systematic review to those CoT studies concerned with the impact of parent and family measures on child outcome. However, some researchers have used CoT data to explore other kinds of research question. For example, some studies have used CoT samples to explore the relative role of genes and environment in the etiology of parenting (Kendler, 1996; Losoya, Callor, Rowe & Goldsmith, 1997; Neiderhiser et al., 2004; Neiderhiser, Reiss, Lichtenstein, Spotts, & Ganiban, 2007). The importance of marital partners as a source of influence on maternal adjustment has also been assessed using CoT data (Spotts et al., 2004; Spotts et al., 2005). Two studies have used CoT samples to examine gift-giving within avuncular relationships as a method of testing evolutionary theories of inclusive fitness (Segal & Marelich, 2011; Segal, Seghers, Marelich, Mechanic, & Castillo, 2007). Although we do not review these articles in full detail here we draw the readers' attention to them as examples of interesting and innovative alternative uses of CoT data.

Another use of CoT data worthy of mention is a slight extension of the typical CoT design involving the use of parent and parent co-twins phenotypes to control for genetic susceptibility and environmental risk when looking at relationships between measured environmental risk factors and offspring outcome (Duncan et al., 2008; Scherrer et al., 2008; Scherrer et al., 2009; Scherrer et al., 2012a; Scherrer et al., 2012b; Sartor et al. 2008; Sartor et al. 2010; Xian et al. 2010). The first example of this approach is a study conducted by Duncan et al. (2008). They were interested in the association between the experience of abuse during childhood and later cannabis abuse/dependence in the offspring of the VETR sample. By using information on the drug dependence history of the (twin) parents Duncan et al. (2008) were able to control for the genetic susceptibility towards drug dependence and the environmental risks associated with having a drug dependent father. Results showed that childhood sexual abuse predicted cannabis abuse/dependence above and beyond the genetic and familial risks associated with having a drug dependent father.

Possible Future Directions

Through their ability to partial out genetic and environmental effects CoT studies have contributed to our understanding of the intergenerational transmission of mental disorders and the relationship between parenting and child outcome. However, there is still a great deal to learn and CoT studies still have more to contribute. For example, as is often the case with behavioral studies, researchers have to date focussed primarily on negative phenotypes (psychopathology, negative parenting etc.), but equally important is the investigation of positive phenotypes such as wellbeing, resilience and ability. Understanding the ways in which parents can and do contribute to the positive development of their children is of clear benefit. In the future, as the relevant technologies become cheaper it may also become feasible for CoT researchers to move beyond the use of questionnaires and interviews and perhaps include physiological measures in their studies such as EEG, fMRI, or endocrinological measures. The inclusion of such measures could assist in elucidating the biological pathways through which behavioral phenotypes are transmitted from one generation to the next.

Although CoT studies have thus far largely focussed on psychological and psychiatric phenotypes, there is no reason why the CoT technique cannot be applied to phenotypes outside these fields of study. To date there have been CoT studies on phenotypes such as birth weight (Magnus et al., 1985; Nance et al., 1983), education (Behrman & Rosenzweig, 2002; Bingley, Christensen & Jensen, 2009), asthma (Havland et al., in press) and income (Amin, Lundborg & Rooth, 2011) but there remains a host of associations between the behavior/traits of one generation and those of the next that could benefit from examination within a CoT framework. Some possibilities might include the hypothesised link between elevated levels of hygiene in childhood and autoimmune disorders (a component of the 'hygiene hypothesis'), or the relationship between the diet a child is fed and their weight, behavior, or ability to concentrate.

To date CoT studies have predominantly used samples of adult twins and their adolescent or adult offspring, often employing retrospective reports to assess childhood phenotypes. However,

collecting and utilising prospective CoT data could be a particularly powerful technique through which to study infant and child development as it happens. Undertaking such a study would of course be logistically challenging (and involve a prolonged period of data collection). One possible way to ease the burden on researchers would be to collect data on the children of twins already enrolled in twin registries. There are many samples of adolescent and young adult twins already in existence who will soon be having children of their own, if indeed they are not already (see the February 2013 special issue of *Twin Research and Human Genetics* for details on many of the twin datasets in existence). Creating CoT studies from such samples would enable the study of early child development. Of course, where adolescent or adult phenotypes are of interest to researchers then the use of samples of adult twins and their children may be preferred.

Sex differences have been noted in some CoT studies, such that parent-child relationships are different for boys compared to girls (D'Onofrio, et al., 2007), or for mothers compared to fathers (Narusyte et al., 2011). Clearly such findings are of interest and may have important consequences for our understanding of parent-child relationships. However, to date many CoT studies have not investigated sex differences. In some instances this may have been because it was not possible, either because of sample composition (i.e. the VETR is all-male) or because of the question being asked (i.e. effects of smoking during pregnancy). In other cases issues of statistical power likely played a part – disaggregating a sample into mother-daughter pairs, mother-son pairs, father-daughter pairs and father-son pairs is always going to reduce power to detect associations. Because males are often less likely to take part in research than females this is more of a problem for some pairings than others. Other issues relate to the independence of comparisons and to nesting: Because mother-child and father-child comparisons will in many cases involve the same child, and because parent-son, parent-daughter comparisons may involve the same parent, comparisons are not independent so father/mother son/daughter models may need to be run separately (e.g. see Narusyte et al., 2011; Marceau et al., 2013). As such 'no-sex differences' models may not strictly speaking be nested within 'sex differences models', making it difficult to formally test them against

one another. All of these difficulties can in some ways be circumvented by using larger samples, running separate mother/father son/daughter models, and comparing confidence intervals in place of formally testing sex differences.

One of the most important findings to come out of CoT research in recent years has been the identification of evocative rGE in parenting/child behavior relationships (Narusyte et al., 2008; 2011). Like adoption studies (e.g. O'Connor et al., 1998; Ge et al., 1996) and twin studies (Klahr & Burt, 2013) showed before them, ECoT studies have demonstrated that genetically influenced child behavior can impact parenting in the same way that parenting can impact child behavior. To date the ECoT models used to investigate this phenomenon can only be used with measures of parenting and not parental characteristics (for the reasons discussed earlier in this article). However, it is conceivable that bidirectional effects may exist between certain parent and child characteristics. For example, depressed people often generate interpersonal stress for themselves – they may be argumentative, socially withdrawn, and receive low levels of social support. This interpersonal stress can itself increase risk for depression. Thus, in a parent-child dyad where one or both are depressed it is easy to see how a cycle could develop in which mother and child may both exacerbate one another's depression (Barker, 2013). To date no CoT studies have investigated bidirectional relationships between parent and child psychopathology. While child-to-parent effects may seem unfeasible for certain relationships (the intergenerational transmission of adolescent conduct disorder for example), for others it is possible and is therefore worthy of investigation. Doing so will however require model development (and longitudinal data) but testing bidirectional hypotheses is likely to be an important step in understanding the relationships between parent and child psychopathology.

It is worth noting that to date most CoT studies have examined bivariate cross-sectional associations between parent and child phenotypes. However, comorbidity between disorders means that multivariate models may be more informative as to the true nature of intergenerational

transmission. A few researchers have explored multivariate CoT analyses (Haber et al. 2010; Volk et al., 2006) but this is an area that requires further development. Volk et al. (2006) showed that although alcohol dependence and nicotine dependence co-occur, and although there is a high degree of genetic overlap between the two, intergenerational transmission seems specific to each. That is, familial risk for nicotine dependence predicted offspring nicotine dependence but not offspring alcohol dependence, and familial risk for alcohol dependence predicted offspring alcohol dependence but not offspring nicotine dependence. To date no multivariate CoT SEMs have been published, however we predict that future model development will allow for the inclusion of more variables in SEM analyses of CoT data.

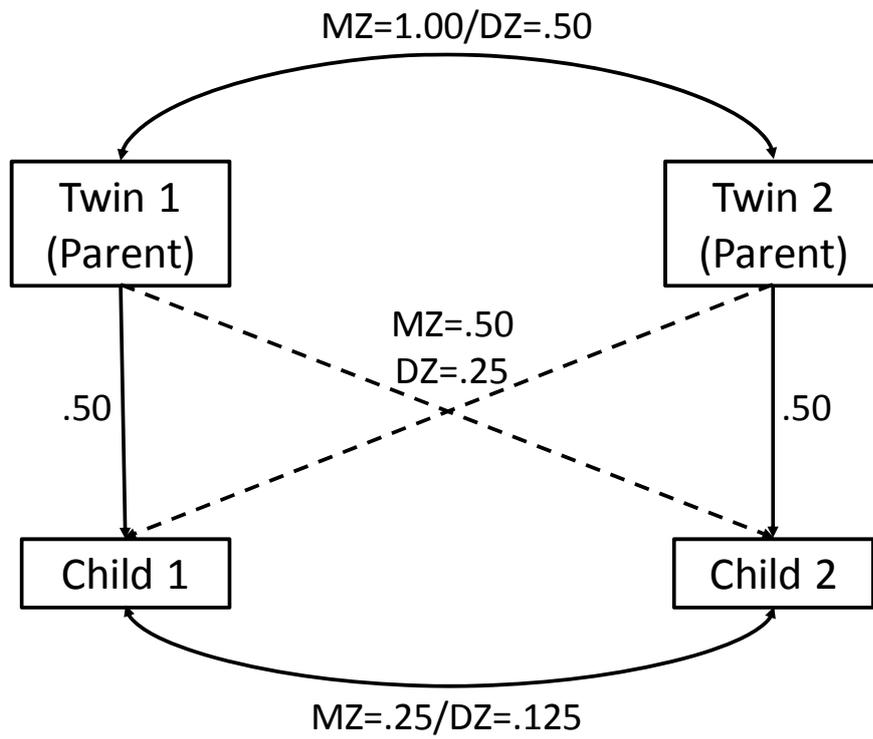
The CoT design can also be combined with other family designs to further study intergenerational associations. We have already mentioned the use of population registries in Scandinavia, which would contain information on not only twin pairs and their offspring but also sibling pairs and half-siblings. It is also possible to combine CoT designs with other extended twin family designs. For example, by including not only the offspring of twins but also their parents, siblings, spouses, and cousins, it is possible to build rich and informative datasets that allow for the estimation of many complex genetic and environmental effects and interactions without making some of the assumptions that other twin designs make (D'Onofrio, Eaves, Murrelle, Maes, & Spilka, 1999; Keller et al., 2009; Maes, Neale, & Eaves, 1997; Truett et al., 1994).

Summary

We believe this article to be an important reminder of a powerful technique. The CoT method is able to control for familial confounds and thus assess potential causality in parent-child relationships in a way that is simply not possible in standard epidemiological studies. There are still a great many research questions yet to be assessed using the CoT technique. Although numerous CoT studies have

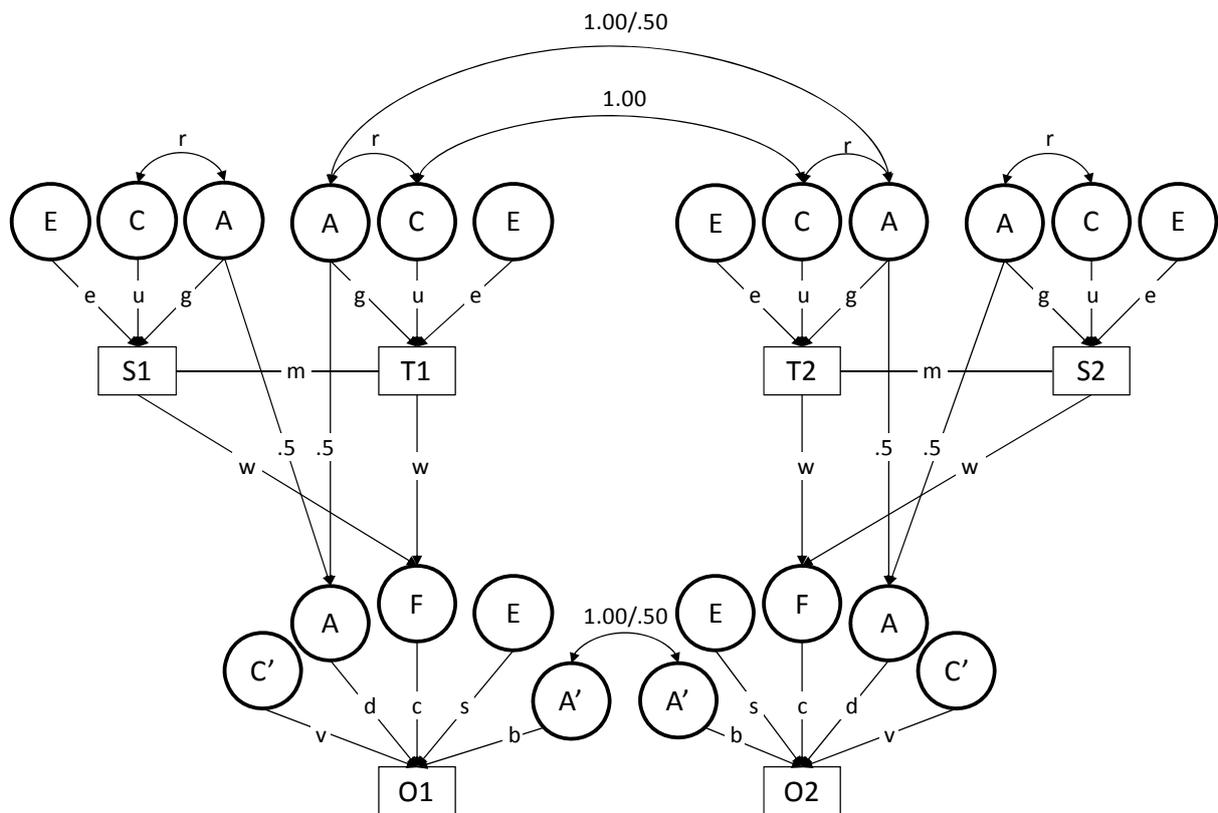
been undertaken the majority have been focussed within a handful of CoT samples. There are many more twin samples that await conversion to CoT samples (and indeed many twins not currently involved in research who could become part of a CoT study). In the coming years several large twin samples already in existence will begin to have children of their own. This presents researchers with opportunities to conduct novel and exciting studies into the relationships between parent and child phenotypes. We hope that this review will be of use to researchers interested in employing CoT techniques in their own research.

Figure 1. Genetic correlations for twin pairs and their children



Note: MZ=Families with monozygotic twins as parents; DZ=Families with dizygotic twins as parents

Figure 2. Children-of-twins structural model with spouse included. From Silberg et al. (2010)



Note: The squares represent twin 1 (T1), twin 2 (T2), spouse of twin 1 (S1), spouse of twin 2 (S2), offspring of twin 1 (O1), offspring of twin 2 (O2). The circles represent the latent etiological factors: A, additive genetic effects expressed in both adults and children (life-course persistent); A', residual additive genetic effects specific to children (juvenile limited); C, shared environmental effects adults; C', residual, juvenile-specific, shared environmental effects in twins and siblings; E, adult unique environmental effect; E' child unique environmental effect; F, shared environmental effects on children explained by parental phenotype. The paths estimate the influences of the latent genetic and environmental factors: g (genetic influence on parent trait), e (nonshared environmental influence on parent trait), u (shared environmental influence on parent trait), m (relationship between twin and spouse traits), w (effect of parent trait on child environment), c (direct environmental influence of parent trait on child), d (genetic influence on child trait shared with parent trait), v (shared environmental influence specific to child trait), s (nonshared environmental influence on child trait), b (genetic influence specific to child trait).

reflects the direct environmental effect of parenting on child adjustment, whereas path n denotes evocative processes in the relationship. Significant paths m , $a1'$, and $a1$ indicate passive rGE , whereas evocative rGE is suggested by significant n , $a1'$, and/or $a2$.

Table 1. Genetic and shared environment correlations

Familial Pair	Genetic	Shared	Shared
	Correlation	Environment	Environment
		Correlation	Correlation
		(Nuclear Family)	(Extended Family)
MZ twin pair	1.00	1.00	1.00
DZ twin pair	.50	1.00	1.00
Full Siblings	.50	1.00	1.00
Half-siblings living together	.25	1.00	1.00
Half-siblings living apart	.25	0	0
Unrelated siblings living together	.00	1.00	1.00
Parent-child	.50	1.00	1.00
Aunt/Uncle – Niece/Nephew (parents are MZ twins)	.50	0	1.00
Aunt/Uncle – Niece/Nephew (parents are DZ twins or full siblings)	.25	0	1.00
Cousins (MZ parents)	.25	0	1.00
Cousins (DZ/full sibling parents)	.125	0	1.00

Table 2. Intra-familial correlations in children-of-twins studies. MZ correlations in upper quadrant, DZ correlations in lower quadrant.

	Parent (twin) 1	Parent (twin) 2	Child 1	Child 2
Parent (twin) 1	-	MZpp	MZpc	MZav
Parent (twin) 2	DZpp	-	MZav	MZpc
Child 1	DZpc	DZav	-	MZcc
Child 2	DZav	DZpc	DZcc	-

Note: Parents are twins. MZ twin family correlations are given above the diagonal, DZ twin family correlations are given below the diagonal. Child 1 is the offspring of parent 1, child 2 is the offspring of parent 2. MZpp=correlation between MZ twins (parents); MZpc=correlation between MZ parent and child; MZav= MZ avuncular correlation; MZcc=correlation between cousins (MZ family); DZpp=correlation between DZ twins (parents); DZpc=correlation between DZ parent and child; DZav= DZ avuncular correlation; DZcc=correlation between cousins (DZ family).

Assuming that the designation of twin 1 and twin 2 is random, any differences in parent-child correlations within zygosity (i.e. the correlation between parent 1 and child 1 compared to that of parent 2 and child 2) will be due to sampling error. Similarly, no major differences in parent-child correlations between zygosity (MZ vs. DZ) should be expected. This is because the parental phenotype of an MZ twin should have no more/less of an effect on their child than that of a DZ twin (furthermore, any differences would have no clear implications for the likely nature of intergenerational transmission given that genetic correlations are .50 in both instances).

Table 3. 'Children- of-twins' studies

Authors	Sample(s)	Design	Environmental Measure/ Parental Attribute	Outcome / Child Attribute	Control Variables	Genetic Overlap?	Environmental Effect?*	rGE?
Class et al., 2012	Twin Offspring Study of Sweden: 852 same- sex twin pairs, their spouse and child (offspring mean age = 16; range 11-22)	CoT	Depressive symptoms CESD self-report scale	Perceived self-competence Self-report Harter Perceived Competence Scale	Family SES, parental education, offspring age and sex	Mothers: Yes Fathers: No	No Yes	Yes No
Coyne et al., 2012	Swedish national registries: 79,545 sister pairs with 337,880 offspring, 3,352 twin pairs with 7,042 offspring	CoT	Maternal age at first birth	Antisocial behaviour History of criminal convictions	Parental history of criminal convictions, parental education, offspring gender, birth order, paternal age at birth	No	Yes	No
D'Onofrio et al., 2003	Virginia Twin Registry & the Norwegian Twin Panel: 1,004 pairs female twins, 1,435 offspring	CoT	Smoking During Pregnancy (none, <10 per day, 10-20, 20+)	Birth Weight (kg)	Twins & spouses: BMI and general smoking, Mothers drinking during pregnancy, Children: birth order of child, gestational age.	No	Yes	No
D'Onofrio et al., 2005	Australian Twin Registry: 1,409 adult twins, their spouses and 2,554 of their young adult children (offspring mean age = 25; range 14-39)	CoT	Marital Instability Lifetime history of divorce or marital separation, including separation from a cohabiting relationship	Offspring psychopathology 3 factors identified by exploratory factor analysis of items assessing DSM-IV disorders: Drug & Alcohol Use, abuse and dependence of alcohol, cigarettes and drugs. Behavioural Problems CD, ODD, ADHD, legal problems due to alcohol use. Internalising Depression and suicidal ideation	Twins & spouses: psychopathology, drug and alcohol problems, smoking, suicidality, age at birth of first child, education. Offspring: age, gender.	No No No	Yes Yes Yes	No No No

D'Onofrio et al., 2006	Australian Twin Registry: 1,409 adult twins and 2,554 of their young adult children (offspring mean age 25; range 14-39)	CoT	Marital Divorce Lifetime history of divorce and marital separation	Education Age at first sexual intercourse Cohabitation Substance use Internalising problems all measured using the Structured Assessment for the Genetics of Alcoholism.	Twins: Education, age at birth of first child, No. lifetime symptoms/diagnoses of conduct disorder, alcohol abuse, smoking, depression, lifetime history of substance use, suicidality.	No Yes Yes Yes Yes	Yes Yes No Yes Yes	No Yes Yes Yes Yes
D'Onofrio, Turkheimer, Emery, Maes et al., 2007	The Virginia 30,000: 14,763 twins/twin relative respondents including 4,391 spouses and 4,800 offspring (offspring mean age 36; range 16-79)	CoT	Marital Instability A composite of self-reported marital status, date of separation (if separated), years with current partner, and no. times married	Alcohol Problems lifetime history of problems (diagnosis or treatment by physician). Internalising Problems measured by the SCL (individuals in the top 20% considered high on emotional problems)	Twins & spouses: Education, alcohol use, lifetime alcohol problems, lifetime cigarette use, emotional difficulties (measured by SCL) and lifetime history of depression.	No Yes	Yes No	No Yes
D'Onofrio, Slutske et al., 2007	Australian Twin Registry: 889 twin families, including spouses and 2,554 young adult children (offspring mean age = 25; range 14-39)	CoT	Conduct problems DSM-III-R diagnosis and symptoms of CD prior to the age of 18, as measured using the Semi-Structured Assessment for the Genetics of Alcoholism.	Conduct Problems DSM-III-R diagnosis and symptoms of CD prior to the age of 18, as measured using the Semi-Structured Assessment for the Genetics of Alcoholism.	Twins & spouses: Lifetime symptoms for alcohol abuse, cigarette use, illegal substance use, suicidality, depression, age at birth of first child, level of education, lifetime history of divorce/separation.	Females: Yes Males: No	No Yes	Yes No
D'Onofrio, Turkheimer, Emery, Harden et al., 2007	Australian Twin Registry: 836 twin families, including spouses and 2,334 offspring (offspring mean age = 25; range 14-39)	CoT	Marital Instability lifetime history of divorce or marital separation, including separation from a cohabiting relationship	Marital Instability lifetime history of divorce or marital separation, including separation from a cohabiting relationship	Twins & spouses: Education, church attendance, age at birth of first child, Lifetime symptoms/diagnoses of conduct disorder, alcohol abuse, depression, lifetime history of substance use, suicidality.	Yes	Yes	Yes
Duncan et al., 2006	Vietnam Era Twin Registry: 512 twin fathers, 877 offspring (age range 12-26) and	CoT	Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study)	Alcohol Use Abuse/Dependence Semi-Structured Assessment for the Genetics of Alcoholism interview: DSM-IV criteria	Twin fathers: employment status, race, illicit substance abuse. Mothers: alcohol abuse/dependence. Parents:	No	No	No

	507 mothers		interview) and DSM-IV alcohol abuse and dependence (assessed by Lifetime Drinking History) during the first 12 years of the offspring's life		psychopathology, education, family income. Offspring: age at first drink, age, gender, DSM-IV psychopathology, drug use.			
Duncan et al. 2008	Vietnam Era Twin Registry: 725 twin fathers, 427 mothers and 839 offspring (offspring mean age 23)	CoT	Paternal Illicit Drug Dependence Lifetime history and DSM-III-R criteria (assessed by Harvard Drug Study interview)	Cannabis abuse/dependence Semi-Structured Assessment for the Genetics of Alcoholism interview: DSM-IV criteria		Unable to distinguish G from E		
Fischer, 1971	21 pairs of same-sex MZ twins born in Denmark between 1870 and 1920; 72 children	MZ CoT	Schizophrenia diagnosis (or schizophrenia-like symptoms)	Schizophrenia, schizophrenia-like psychosis and suicide	None of the spouses were themselves diagnosed with psychosis	Yes	No	Yes
Glowinski et al., 2004	Vietnam Era Twin Registry: 1,212 twin fathers, their spouses and 1270 offspring (offspring mean age 19; range 12-26)	CoT	Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study interview) and DSM-IV alcohol abuse and dependence (assessed by Lifetime Drinking History)	Suicidal behaviours lifetime suicidal ideation, suicide plans, and suicide attempts (assessed by Semi-Structured Assessment for the Genetics of Alcoholism Interview).	Twin fathers: substance abuse/dependence, employment, income, antisocial personality disorder. Mothers: alcohol abuse/dependence. Both parents: major depressive disorder, education, marital status. Offspring: age, gender, ethnicity	No significant phenotypic association	-	No
Gottesman & Bertelsen, 1989	18-year follow-up of Fischer's (1971) twins: 68 pairs	CoT	Schizophrenia ICD-8 diagnosis	Schizophrenia ICD-8 diagnosis	None of the spouses were themselves diagnosed with psychosis	Yes	No	Yes
Haber et al., 2005	Vietnam Era Twin Registry: 1,212 twin fathers, 862 spouses and 1270 offspring (offspring mean age 19; range 12-26)	CoT	Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study interview) and DSM-IV alcohol abuse and dependence (assessed by Lifetime Drinking History)	Conduct disorder DSM-IV symptoms were used: 0-1; 2; 3; 4+ as identified with the Semi-Structured Assessment for the Genetics of Alcoholism interview	Twin fathers: employment, income, drug abuse, dysthymia, anxiety, panic and posttraumatic stress disorders. Mothers: alcohol abuse/dependence. Both parents: antisocial personality disorder, conduct disorder, education, depression, marital status. Offspring: age, gender, ethnicity.	Suggestive	No	No

Haber et al., 2010	Vietnam Era Twin Registry: 1,774 male-male twin pairs, 1202 spouses and 1917 offspring (offspring mean age 21)	CoT	Drug Dependence Lifetime drug use history Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study interview) and DSM-IV alcohol abuse and dependence (assessed by Lifetime Drinking History)	Conduct disorder DSM-IV symptoms were used: 0-1; 2; 3; 4+ as identified with the Semi-Structured Assessment for the Genetics of Alcoholism interview	Twin fathers: drug abuse, depression, dysthymia, anxiety, panic and posttraumatic stress disorders, employment. Mothers: alcohol abuse, alcohol dependence, depression, marijuana use. Both parents: antisocial personality disorder, conduct disorder, education, marital status, household income. Offspring: age, gender, ethnicity	Yes Yes	Yes No	Yes Yes
Harden, Lynch et al., 2007	Australian Twin Registry: 712 female twins, their spouses, 1,368 offspring (offspring mean age 25; range 14-39)	CoT	Adolescent motherhood defined as being ≤ 20 years old at time of childbirth.	Offspring Adjustment Exploratory factor analysis of DSM-IV symptoms using Semi-Structured Assessment for the Genetics of Alcoholism interview. 3 factors were identified: Drug & Alcohol Use , abuse and dependence of alcohol, cigarettes and drugs. Externalising CD, ODD, ADHD, legal problems due to alcohol use. Internalising Depression and suicidal ideation	Propensity weights were created to weight the sample (at the twin family level) to account for selection bias. Parental psychiatric history and sociodemographic variables.	No (not sig. but evidence)	Yes	No
Harden, Turkheimer et al., 2007	Australian Twin Registry: 1,045 twins, 2,051 offspring (offspring mean age 25; range 14-39)	CoT	Marital conflict Children reported on marital conflict of their parents in Semi-Structured Assessment for the Genetics of Alcoholism interview.	Conduct problems Child reported incidence of DSM-III-R symptoms in Semi-Structured Assessment for the Genetics of Alcoholism interview.	Propensity weights were created to weight the sample (at the twin family level) to account for selection bias. Parental psychiatric history and sociodemographic variables.	Yes	No	Yes
Havland et al., 2013	Twin and Offspring Study of Sweden: 1691 mother-adolescent child dyads, including 1057	CoT	Maternal Anxiety Self-reported using the Karolinska Scales of Personality and the Beck Anxiety Inventory (BAI)	Asthma Maternal and self-reported asthma from the Child behavior Check List and the Physical Symptoms Inventory. Asthma	Offspring: sex, birth year. Mothers: smoking, twins zygosity, birth weight, preterm birth, caesarean section, smoking during pregnancy, maternal education, maternal	Only significant phenotypic associations were between	No strong evidence	Possibly

	twins and 624 spouses. (Offspring mean age 16; range 11-22)			diagnosis and medication were also ascertained from the National Patient Register and the Prescribed Drug Register	asthma diagnosis and asthma medication	BAI and child self-report: Familial confounding detected			
Jacob et al., 2003	Vietnam Era Twin registry: 1,213 male twins, 862 mothers, 1,270 offspring (offspring mean age 19; range 12-26)	CoT	Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study interview) and DSM-IV alcohol abuse and dependence (assessed by Lifetime Drinking History)	Alcohol Abuse & Dependence Semi-Structured Assessment for the Genetics of Alcoholism interview: DSM-IV lifetime and current diagnoses of alcohol abuse and alcohol dependence	Twin fathers: employment, income, drug abuse, dysthymia, anxiety, panic and posttraumatic stress disorders. Mothers: alcohol abuse/dependence. Both parents: antisocial personality disorder, conduct disorder, education, depression, marital status. Offspring: age, gender, ethnicity.	Suggestive	Suggestive	Yes	
Knopik et al., 2006	Australian Twin registry: 268 twin pairs, 922 children (mean age 16)	CoT	Maternal Alcoholism Semi-Structured Assessment for the Genetics of Alcoholism interview used to identify those with a history of DSM-IV alcohol abuse/dependence.	ADHD problems Diagnostic Interview for Children and Adolescents and the Semi-Structured Assessment for the Genetics of Alcoholism interview. DSM-IV ADHD diagnoses based on mother reported symptoms. 6 or more symptoms=ADHD.	Twin mothers: Prenatal smoking, age, drinking during pregnancy , Both parents: psychiatric and substance use problems, education, family income, marital status. Offspring: age, gender, no. of siblings.	Suggestive	No	No	
Knopik et al., 2009	Vietnam Era Twin Registry: 727 twin fathers, 732 spouses and 1,116 offspring (offspring mean age 19)	CoT	Paternal Alcoholism DSM-III-R alcohol dependence (assessed by Harvard Drug Study interview)	ADHD problems Diagnostic Interview for Children and Adolescents and the Semi-Structured Assessment for the Genetics of Alcoholism interview. DSM-IV ADHD diagnoses based on mother reported symptoms. 6 or more symptoms=ADHD.	Twin fathers: Education. Both parents: age, psychopathology, SES, income, marital status, no. of offspring.. Offspring: prenatal nicotine and alcohol exposure (mothers' smoking/drinking in pregnancy).	Suggestive	No	No	
Kringlen (1987)	65 offspring of MZ twin pairs discordant for schizophrenia	MZ CoT	Schizophrenia clinical diagnosis via a structured interview	Schizophrenia		Yes	No	Yes	
Lynch et al., 2006	Australian twin registry: 887 pairs	CoT	Harsh Punishment Retrospective report by the	Offspring Adjustment Exploratory factor analysis of	Twin parent: depression, drug use, alcohol use, age, gender, SES,				

	and 2,554 children. (offspring mean age = 25; range 14-39) Over-selection of divorced, alcohol dependent, conduct disordered, depressed twins.		offspring. Five punishment groups created: nonphysical mild; physical mild; nonphysical harsh; physical harsh; no punishment	DSM-IV symptoms using Semi-Structured Assessment for the Genetics of Alcoholism interview. 3 factors identified: Drug & Alcohol Use, abuse and dependence of alcohol, cigarettes and drugs. Externalising CD, ODD, ADHD, legal problems due to alcohol use. Internalising Depression and suicidal ideation	divorce status. Offspring: age, gender.	Evidence for confounding. Could be genetic or shared environment	Yes (physical harsh) Yes (physical harsh) Yes (physical harsh)	No No No
Magnus et al., 1985	Norwegian Twin Panel: 662 female twin pairs; 162 discordant for smoking	CoT	Smoking during pregnancy Categorised if smoked daily during at least one of the reported pregnancies	Birth weight Ascertained by linking with The Medical Birth Registry	Mothers: alcohol consumption, caffeine consumption, age at menarche, height and weight of twins, socioeconomic status, level of education	No	Yes	No
Marceau et al., 2013	Twin and Offspring Study of Sweden: 854 twin families (parents-as-twins; offspring mean age 16; range 11-22) and Nonshared Environment in Adolescent Development: 405 twin families (children-as-twins; mean age 16; range 11-22)	ECoT	Negative Parenting Composite (mother, father and adolescent) scores on the conflict subscale of Parent-Child Relationships Questionnaire (Hetherington & Clingempeel, 1992) and the coercive and punitiveness subscales of the Parent Discipline Behaviour Inventory (Hetherington & Clingempeel, 1992)	Externalising Problems Multi-rater (mother, father, adolescent) composite scores. In the NEAD sample the Zil was used (Zill, 1988). In TOSS the CBCL/YSR was used (Achenbach, 1991)	Children: age, sex, age difference (in NEAD non-twin siblings)	No	No	Ext. behaviour evoked negative parenting
McCutcheon et al., <i>in press</i>	Vietnam Era Twin Registry: 488 twin fathers, 420 biological mothers, and 831 offspring (offspring	CoT	Substance Use Lifetime history of DSM-III-R diagnoses of alcohol and drug dependence derived by Harvard Drug Study	Psychiatric and Substance Use Disorders 4 latent classes (derived from Semi-Structured Assessment for the Genetics of Alcoholism	Offspring: early environment, history of child abuse, perceptions of sibling substance use offspring perception of friends' substance use, age, ethnicity, gender. Parents:	Unable to distinguish between genetic and environmental	-	-

	mean age 23)		interview	interview responses): Unaffected	psychiatric disorder,,education, household income, divorce status.		transmission.	
				Alcohol Use/Dependence				
				Alcohol and internalising problems				
				Substance use and conduct disorder				
Mendle et al., 2006	Australian Twin Registry: 889 twin pairs, 2,544 offspring (offspring mean age 25; range 14-38)	CoT	Family structure Presence of a non-related adult male during childhood	Age at menarche Retrospective self-report	Child stress, maternal age at menarche.	Possibly: there is evidence for a familial confound	No	No
Narusyte et al. 2008	Twin Offspring Study of Sweded: 539 female twin pairs and one of their offspring (offspring mean age 16; range 11-20). Twin Study of Child and Adolescent Development (TCHAD): 874 adolescent twin pairs and their mothers (twins mean age 17)	ECoT	Maternal Emotional Over-Involvement: Parent report on the EOI scale of the Expressed Emotion Measure (Hansson & Jarbin, 1997)	Internalising Problems: Child report on the YSR version of the CBCL (Achenbach, 1991)	Corrected for child age and gender.	Yes	No	E-rGE
Narusyte et al. 2011	Twin Offspring Study of Sweden: 909 pairs adult twins and 1818 children (mean age 16. TCHAD: 915 pairs twin children and their parents	ECoT	Parental criticism Parental report on the Critical Remarks subscale of the Expressed Emotion measure (Hanson & Jarbin, 1997)	Externalising behaviour Youth Self Report version of the CBCL (Achenbach, 1991)	Child sex and age. Twin sex and parental criticism of the spouse.	Fathers: No Mothers: Yes	Fathers: Yes Mothers: No	P-rGE E-rGE

Schermerhorn et al., 2011	Twin Offspring Study of Sweden: 867 twin pairs, their spouses 1734 offspring (offspring mean age 16; range 11-22)	CoT	<p>Family conflict Twins, spouses and children all completed the Family Conflict Subscale of the Family Environment Scale (Moos & Moos, 1981)</p> <p>(low) Marital Quality Twins and spouses completed the dyadic adjustment scale (Spanier, 1976)</p> <p>Marital (dis)agreement about parenting Twins and spouses completed the Agreement on Parenting measure (Reiss et al., 2000)</p>	<p>Externalising Problems Internalising Problems Children reported using the CBCL (Achenbach & Edelbrock, 1976)</p> <p>Sensitivity test also run for family conflict: child-only and parent-only report</p>	Twin education, spouse education, SES.	Ext.: No Int.: No	Ext.: Yes Int.: Yes	No No
						Ext.: Yes Int.: No	Ext.: No Int.: Yes	Yes No
						Ext.: Yes Int.: No	Ext.: Yes Int.: Yes	Yes No
Silberg et al., 2010	Mid Atlantic Twin Registry: 1043 twin pairs with at least one child (offspring mean age 14; range 9-17) Virginia Twin Study of Adolescent Behavioural Development (VTSABD): 1412 juvenile twin pairs and their parents (twins mean age 12; 8-18)	CoT	<p>Depressive Symptoms Self-report. Short MFQ</p> <p>Measured in twin and spouse.</p>	<p>Depressive Symptoms Self-report. Short Mood and Feelings Questionnaire</p> <p>Conduct Problems Maternal report. Rutter 'A' scale (same scales in both samples)</p>	Full model includes spousal depression and uses this information to account for assortative mating (on depression)	No Yes	Yes Yes	No Yes
Silberg et al., 2012	Mid Atlantic twin Registry: 856 twin pairs and 1,290 spouses with at least	CoT	<p>Antisocial behaviour measured in adult twins and their spouses as part of a more extensive interview</p>	<p>Conduct Disturbance Maternal ratings on the Rutter A scale</p> <p>Hyperactivity</p>	Full model includes spousal depression and uses this information to account for assortative mating (on antisocial	Yes Yes	Yes No	Yes Yes

	one child between the ages of 9 and 17 (mean age 13). VTSABD: 1,413 twin pairs and their parents (twins mean age 12; range 8-18)		used to diagnose antisocial personality disorder	Maternal ratings on the Rutter A scale Depressive Symptoms Self-report. Short Mood and Feelings Questionnaire	behaviour)	No	Yes	No
Singh et al. 2011	Australian Twin Registry: 889 twin families: 1296 twins, 1046 spouses, and 2555 offspring (offspring mean age 25; range 14-39)	CoT	Depression Semi-Structured Assessment for the Genetics of Alcoholism interview used to identify those with DSM-III-R MDD	Depression SSAGA used to identify those with DSM-III-R MDD Conduct Disorder SSAGA used to identify those with DSM-III-R CD prior to age 18 (retrospective report)	Parents: history of divorce, age at first childbirth, education, conduct disorder, substance use and alcohol dependence or abuse. Sampling weights also used. Offspring: age, gender.	No Yes	Yes No	No Yes
Slutske et al., 2008	Australian Twin Registry: 836 twin pairs, 983 spouses and 2334 offspring (offspring mean age 26; range 18-39)	CoT	Alcoholism Semi-Structured Assessment for the Genetics of Alcoholism interview used to identify continuous (lifetime) symptom count of alcohol use disorder, and lifetime diagnosis of alcohol dependence – coded for DSM-IV based on DSM-III-R symptoms.	Alcohol use disorder Semi-Structured Assessment for the Genetics of Alcoholism used to identify continuous (lifetime) symptom count of alcohol use disorder – DSM-IV, excluding those items not present in DSM-III-R (for consistency with twin ratings)	Parents: demographics, other substance use, cigarette smoking, psychopathology, educational attainment, age at birth of first child, church attendance, history of divorce, lifetime history of suicidality. Sampling weights also used. Offspring: age, gender.	No	No	No
Volk et al. 2007	Vietnam Era Twin Registry: 1,213 win fathers, 862 biological mothers and 1,270 offspring (offspring mean age 19; range 12-26)	CoT	Alcohol Dependence Diagnostic Interview Schedule used to diagnose lifetime DSM-III-R AD Nicotine Dependence Diagnostic Interview Schedule used to diagnose lifetime DSM-III-R ND	Alcohol Dependence Semi-Structured Assessment for the Genetics of Alcoholism interview used to diagnose lifetime DSM-III-R AD Nicotine Dependence Semi-Structured Assessment for the Genetics of Alcoholism interview used to diagnose lifetime DSM-III-R ND	Mothers: lifetime AD and ND. Offspring: age, gender, maternal reports of offspring ADHD and ODD, offspring-reported internalising and externalising disorders.	Unable to distinguish G from E Yes	- No	- Yes
							Bivariate analysis suggests risk	

						is specific		
Authors	Sample(s)	Design	Environmental Measure/ Parental Attribute	Outcome / Child Attribute	Control Variables	Genetic Overlap?	Environmental Effect?*	rGE?
Waldron et al., 2009	2 CoT studies taken from the Australian Twin Registry: MATCH: 617 twin pairs and 1643 adolescent offspring; and PACER: 411 twin pairs and 756 adolescent offspring (combined sample offspring mean age 14)	CoT	Alcoholism Semi-Structured Assessment for the Genetics of Alcoholism interview used to identify continuous (lifetime) symptom count of alcohol use disorder, and lifetime diagnosis of alcohol dependence – coded for DSM-IV based on DSM-III-R symptoms.	Offspring Behaviour Problems Externalising problems Parent report CBCL (Achenbach, 2001) Internalising problems Parent report CBCL (Achenbach, 2001) Total problems Composite of internalising and externalising	Offspring: age, gender.	Yes	No	Yes
						Suggestive	No	No
						Yes	No	Yes
Class et al., 2012	TOSS sample: 909 same-sex twin pairs, their spouse and child	CoT	Depressive symptoms CESD self-report scale	Perceived self-competence Self-report Harter Perceived competence scale	Family SES, parental education, offspring age and sex	Mothers: Yes Fathers: No	No Yes	Yes No
Coyne et al., 2012	Swedish national registries: 79,545 sister pairs with 337,880 offspring, 3,352 twin pairs with 7,042 offspring	CoT	Maternal age at first birth	Antisocial behavior History of criminal convictions	Parental history of criminal convictions, parental education, offspring gender, birth order, paternal age at birth	No	Yes	No

D'Onofrio et al., 2003	Virginia Twin Registry & the Norwegian Twin Panel: 1,004 pairs female twins, 1,435 offspring	CoT	Smoking During Pregnancy (none, 10 per day, 10-20, 20+)	Birth Weight (kg)	Twins & spouses: BMI and general smoking, Mothers drinking during pregnancy, Children: birth order of child, gestational age.	No	Yes	No
D'Onofrio et al., 2005	Australian Twin Registry. 1,409 adult twins, their spouses and 2,554 of their young adult children	CoT	Marital Instability lifetime history of divorce or marital separation, including separation from a cohabiting relationship	3 factors identified by exploratory factor analysis of items assessing DSM-IV disorders: Drug & Alcohol Use Use, abuse and dependence of alcohol, cigarettes and drugs. Behavioral Problems CD, ODD, ADHD, legal problems due to alcohol use. Internalizing Depression and suicidal ideation	Twins & spouses: psychopathology, drug and alcohol problems, suicidality, age at birth of first child, education.	No	Yes	No
D'Onofrio et al., 2006	Australian Twin Registry. 1,409 adult twins, their spouses	CoT	Marital Divorce Lifetime history of divorce and marital separation	Education Age at first sexual intercourse Cohabitation	Twins: Education, age at birth of first child, No. lifetime symptoms/diagnoses of conduct	No	Yes	No
						Yes	Yes	Yes
						Yes	No	Yes

	and 2,554 of their young adult children			Substance use Internalizing problems all measured using the Structured Assessment for the Genetics of Alcoholism.	disorder, alcohol abuse, depression, lifetime history of substance use, suicidality.	Yes Yes	Yes Yes	Yes Yes
D'Onofrio, Turkheimer, Emery, Maes et al., 2007	The Virginia 30,000: Twins (14,763), their spouses and their offspring (4,800)	CoT	Marital Instability A composite of self-reported marital status, date of separation, years with current partner, and no. times married	Alcohol Problems lifetime history of problems (diagnosis or treatment by physician). Internalizing Problems measured by the SCL (individuals in the top 20% considered high on emotional problems)	Twins & spouses: Education, alcohol use, lifetime alcohol problems, lifetime cigarette use, emotional difficulties (measured by SCL) and lifetime history of depression.	No Yes	Yes No	No Yes
D'Onofrio, Slutske et al., 2007	Australian Twin Registry, their spouses, and their young adult children (889 twin families)	CoT	Conduct problems DSM-III-R diagnosis and symptoms of CD prior to the age of 18, as measured using the Structured Assessment for the Genetics of Alcoholism.	Conduct Problems DSM-III-R diagnosis and symptoms of CD prior to the age of 18, as measured using the Structured Assessment for the Genetics of Alcoholism.	Twins & spouses: Lifetime symptoms for alcohol abuse, cigarette use, illegal substance use, suicidality, depression, age at birth of first child, level of education, lifetime history of divorce/separation.	Females: Yes Males: No	No Yes	Yes No
D'Onofrio,	Australian Twin	CoT	Marital Instability lifetime	Marital Instability lifetime	Twins & spouses: Education, church	Yes	Yes	Yes

Turkheimer, Emery, Harden et al., 2007	Registry: 2,334 offspring, nested into 1,224 nuclear families, nested in 836 twin families		history of divorce or marital separation, including separation from a cohabiting relationship	history of divorce or marital separation, including separation from a cohabiting relationship	attendance, age at birth of first child, Lifetime symptoms/ diagnoses of conduct disorder, alcohol abuse, depression, lifetime history of substance use, suicidality.			
Duncan et al., 2006	512 Twin fathers from the Vietnam Era Twin Registry, 877 of their offspring (aged 12-26) and 507 mothers	CoT	Paternal Alcoholism DSM-III-R and DSM-IV alcohol dependence(SSAGA) during the first 12 years of the offspring's life	Alcohol Use Abuse/Dependence Structured Assessment for the Genetics of Alcoholism: DSM-IV criteria	Paternal employment status, race education; Paternal and maternal psychopathology, age at first drink of offspring, age and gender of offspring, offspring DSM-IV psychopathology.	No	No	No
Duncan et al. 2008	725 twin fathers from the VET sample, 427 mothers and 839 offspring (mean age = 23 years)	CoT	Illicit Drug Dependence Lifetime history established using the SSAGA interview and DSM-III-R criteria	Cannabis abuse/dependence Structured Assessment for the Genetics of Alcoholism interview: DSM-IV criteria		Unable to distinguish G from E		
Fischer, 1971	70 pairs of same-sex MZ twins born in Denmark between	MZ CoT	Schizophrenia diagnosis (or schizophrenia-like symptoms)	Schizophrenia, schizophrenia- like psychosis and suicide	None of the spouses were themselves diagnosed with psychosis	Yes	No	Yes

1870 and 1920

Glowinski et al., 2004	Twin fathers from the Vietnam Era Twin Registry, their spouses and children (aged 12-26)	CoT	Paternal alcohol dependence Lifetime Drinking History: Alcohol use, abuse and dependence based on DSM-II-R definitions	Suicidal behaviors lifetime suicidal ideation, suicide plans, and suicide attempts.	Maternal and paternal major depressive disorder and paternal substance abuse/dependence	No significant phenotypic association	-	No
Gottesman & Bertelsen, 1989	18-year follow-up of Fischer's (1971) twins: 68 pairs	CoT	Schizophrenia ICD-8 diagnosis	Schizophrenia ICD-8 diagnosis	None of the spouses were themselves diagnosed with psychosis	Yes	No	Yes
Haber et al., 2005	Vietnam Era Twin Registry. Male-male twin pairs: 1,212 twins, 862 spouses, 1,270 offspring.	CoT	Paternal alcoholism DSM-III-R diagnoses and Lifetime Drinking History instrument identifying alcoholism in both parents.	Conduct disorder DSM-IV symptoms were used: 0-1; 2; 3; 4+ as identified with the Structured Assessment for the Genetics of Alcoholism interview	Maternal/paternal antisocial personality disorder, conduct disorder. Paternal: drug abuse, depression, dysthymia, anxiety, panic and posttraumatic stress disorders. Maternal: alcohol abuse, alcohol dependence, depression.	Suggestive	No	No
Haber et al., 2010	Vietnam Era Twin Registry. 1,774 Male-	CoT	Drug Dependence Lifetime drug use history	Conduct disorder DSM-IV symptoms were used: 0-	Maternal/paternal antisocial personality disorder, conduct	Yes	Yes	Yes

	male twin pairs, 1 or more of whom met criteria for DSM-III-R alcohol dependence. Plus control pairs. Children of twins and their biological mothers also included.		Paternal alcoholism DSM-III-R diagnoses and Lifetime Drinking History instrument identifying alcoholism in both parents.	1; 2; 3; 4+ as identified with the Structured Assessment for the Genetics of Alcoholism interview	disorder, education, marital status. Paternal: drug abuse, depression, dysthymia, anxiety, panic and posttraumatic stress disorders, employment, education. Maternal: alcohol abuse, alcohol dependence, depression, marijuana use. Offspring age and sex	Yes	No	Yes
Harden, Lynch et al., 2007	Maternal subsample of the Australian Twin Registry: 1,368 children (aged 14-39 years) of 712 female twins	CoT	Adolescent motherhood defined as being ≤ 20 years old at time of childbirth.	Exploratory factor analysis of DSM-IV symptoms using Structured Assessment for the Genetics of Alcoholism interview. 3 factors were identified: Drug & Alcohol Use Use, abuse and dependence of alcohol, cigarettes and drugs. Externalizing CD, ODD, ADHD, legal problems due to alcohol use.	Propensity weights were created to weight the sample (at the twin family level) to account for selection bias.	No (not sig. but evidence)	Yes	No
						No (not sig. but evidence)	Yes	No

				Internalizing Depression and suicidal ideation		No	Yes	No
Harden, Turkheimer et al., 2007	Australian Twin Registry: 2,051 children (aged 14-39 years) of 1,045 twins	CoT	Marital conflict Children reported on marital conflict of their parents	Conduct problems Child reported incidence of DSM-II-R symptoms.	Propensity weights were created to weight the sample (at the twin family level) to account for selection bias.	Yes	No	Yes
Havland et al., 2013	Twin and Offspring Study of Sweden	CoT	Maternal Anxiety Self-reported using the Karolinska Scales of Personality and the Beck Anxiety Inventory (BAI)	Asthma Maternal and self reported asthma from the Child behavior Check List and the Physical Symptoms Inventory. Asthma diagnosis and medication were also ascertained from the National Patient Register and the Prescribed Drug Register	Child sex, birth year. Mothers smoking, twins zygosity, birth weight, preterm birth, caesarean section, smoking during pregnancy, maternal education, maternal asthma diagnosis and asthma medication	Only significant phenotypic associations were between BAI and child self report:	No strong evidence	Possibly
Jacob et al., 2003	Vietnam Era Twin registry. 1,213 male twins, 1,270 offspring	CoT	Paternal Alcohol Abuse & Dependence Structured Assessment for	Alcohol Abuse & Dependence Structured Assessment for the Genetics of Alcoholism interview:	Maternal: AA, AD, depression. Paternal: depression, antisocial personality disorder, conduct	Suggestive	Suggestive	Yes

	and 1,070 mothers		the Genetics of Alcoholism interview: DSM-IV lifetime and current diagnoses of alcohol abuse and alcohol dependence	DSM-IV lifetime and current diagnoses of alcohol abuse and alcohol dependence	disorder, drug abuse and dependence, marital status, education, employment status. Offspring: age and sex.			
Knopik et al., 2006	Australian Twin registry: Female twin pairs selected in which at least one twin has history of alcohol problems. 268 twin pairs and 922 of their children.	CoT	Maternal Alcoholism Structured Assessment for the Genetics of Alcoholism interview used to identify those with a history of DSM-IV alcohol abuse/dependence.	ADHD problems Diagnostic Interview for Children and Adolescents and the Structured Assessment for the Genetics of Alcoholism interview. DSM-IV ADHD diagnoses based on mother reported symptoms. 6 or more symptoms=ADHD.	Prenatal smoking, sociodemographic risk/protective factors, parental psychiatric and substance use problems. Drinking during pregnancy	Suggestive	No	No
Knopik et al., 2009	VETR: 727 twin fathers, 732 spouses and 1,116 of their children.	CoT	Paternal Alcoholism Diagnostic interview identifying those with a history of DSM-III-R alcohol dependence.	ADHD problems DSM-IV ADHD symptom count, child report and mother report	Prenatal nicotine and alcohol exposure, SES, parental psychopathology (twin and spouse)	Suggestive	No	No
Kringlen (1987)	65 offspring of MZ twin pairs discordant	MZ CoT	Schizophrenia clinical diagnosis via a	Schizophrenia		Yes	No	Yes

	for schizophrenia		structured interview					
Lynch et al., 2006	Australian twin registry: 887 pairs and 2,554 children. Over-selection of divorced, alcohol dependent, conduct disordered, depressed twins.	CoT	Harsh Punishment Retrospective report by the offspring. Five punishment groups created: nonphysical mild; physical mild; nonphysical harsh; physical harsh; no punishment	Exploratory factor analysis of DSM-IV symptoms using Structured Assessment for the Genetics of Alcoholism interview. 3 factors identified: Drug & Alcohol Use Use, abuse and dependence of alcohol, cigarettes and drugs. Externalizing CD, ODD, ADHD, legal problems due to alcohol use. Internalizing Depression and suicidal ideation	Parental depression, parental drug use, parental alcohol use, age, child gender, parent gender, SES and divorce status.	Evidence for confounding. Could be genetic or shared environment	Yes (physical harsh) Yes (physical harsh)	No No
Magnus et al., 1985	341 MZ and 321 DZ female twin pairs taken from the Norwegian Twin	CoT	Smoking during pregnancy	Birth weight	Alcohol consumption, caffeine consumption, age at menarche, height and weight of twins, socioeconomic status, level of	No	Yes	No

Panel			education					
Marceau et al., 2013	TOSS: 854 twin families (parents-as-twins) and NEAD: 405 twin families (children-as-twins)	ECoT	Negative Parenting Composite (mother, father and adolescent) scores on the conflict subscale of Parent-Child Relationships Questionnaire (Hetherington & Clingempeel, 1992) and the coercive and punitiveness subscales of the Parent Discipline Behavior Inventory (Hetherington & Clingempeel, 1992)	Externalizing Problems Multi-rater (mother, father, adolescent) composite scores. In the NEAD sample the Zil was used (Zill, 1988). In TOSS the CBCL/YSR was used (Achenbach, 1991)	Child sex and age. Twin sex and	No	No	Ext. behavior evoked negative parenting
McCutcheon et al., 2013	Vietnam Era Twin Registry: 488 twin fathers, 420 biological mothers, and 831 offspring	CoT	Substance Use Lifetime history of DSM-III-R diagnoses of alcohol and drug dependence derived by interview	Latent Classes (derived from Structured Assessment for the Genetics of Alcoholism interview responses) Alcohol Use/Dependence	Offspring early environment, , offspring history of child abuse, parental psychiatric disorder, offspring perceptions of sibling substance use, offspring perception of friends substance use, age,	Unable to distinguish between genetic and environmental transmission.	-	-

				Alcohol and internalizing problems	ethnicity, gender, parental education, household income.			
				Substance use and conduct disorder				
Mendle et al., 2006	Australian Twin Registry: 2,544 offspring (ages 14-38) from 889 twin pairs	CoT	Family structure – presence of a non-related adult male	Age at menarche Retrospective self-report	Child stress, maternal age at menarche	Possibly: there is evidence for a familial confound	No	No
Narusyte et al. 2008	TOSS: 539 female twin pairs and one of their offspring. TCHAD: 874 adolescent twin pairs and their mothers	ECoT	Maternal Emotional Over-Involvement: Parent report on the EOI scale of the Expressed Emotion Measure (Hansson & Jarbin, 1997)	Internalizing Problems: Child report on the YSR version of the CBCL (Achenbach, 1991)		Yes	No	E-rGE
Narusyte et al. 2011	Twin Offspring Study of Sweden (909 pairs adult twins) & TCHAD (915 pairs twin	ECoT	Parental criticism Parental report on the Critical Remarks subscale of the Expressed Emotion	Externalizing behavior Youth Self Report version of the CBCL (Achenbach, 1991)	Child sex and age. Twin sex and parental criticism of the spouse.	Fathers: No Mothers: Yes	Fathers: Yes Mothers: No	P-rGE E-rGE

	children)		measure (Hanson & Jarbin, 1997)					
Schermerhorn et al., 2011	TOSS: 867 twin pairs and their spouses and one offspring per twin	CoT	Family conflict Twins, spouses and children all completed the Family Conflict Subscale of the Family Environment Scale (Moos & Moos, 1981) (low) Marital Quality Twins and spouses completed the dyadic adjustment scale (Spanier, 1976) Marital (dis)agreement about parenting Twins and spouses completed the Agreement on Parenting measure (Reiss et al., 2000)	Externalizing Problems Internalizing Problems Children reported using the CBCL (Achenbach & Edelbrock, 1976)	Twin education, spouse education, SES. Sensitivity test also run for family conflict: child-only and parent-only report	Ext.: No Int.: No	Ext.: Yes Int.: Yes	No No
						Ext.: Yes Int.: No	Ext.: No Int.: Yes	Yes No
Silberg et al.,	Mid Atlantic Twin	CoT	Depressive Symptoms	Depressive Symptoms	Full model includes spousal	No	Yes	No

2010	Registry: 1043 twin pairs with at least one child. VTSABD: 1412 juvenile twin pairs		Self-report. Short MFQ Measured in twin and spouse.	Self-report. Short Mood and Feelings Questionnaire Conduct Problems Maternal report. Rutter 'A' scale (same scales in both samples)	depression and uses this information to account for assortative mating (on depression)	Yes	Yes	Yes
Silberg et al., 2012	Mid Atlantic twin Registry: 856 twin pairs with at least one child between the ages of 9 and 17 plus 1,290 spouses. VTSABD: 1,413 twin pairs aged 8-18	CoT	Antisocial behavior measured in adult twins and their spouses as part of a more extensive interview used to diagnose antisocial personality disorder	Conduct Disturbance Maternal ratings on the Rutter A scale Hyperactivity Maternal ratings on the Rutter A scale Depressive Symptoms Self-report. Short Mood and Feelings Questionnaire	Full model includes spousal depression and uses this information to account for assortative mating (on antisocial behavior)	Yes Yes No	Yes No Yes	Yes Yes No
Singh et al. 2011	Australian Twin Registry: 889 twin families: 1296 twins, 1046 spouses, and 2555 offspring	CoT	Depression Structured Assessment for the Genetics of Alcoholism interview used to identify those with DSM-III-R MDD	Depression SSAGA used to identify those with DSM-III-R MDD Conduct Disorder SSAGA used to identify those with DSM-III-R CD prior to age 18	Twin and spouse history of divorce, age at first childbirth, education, parental CD, substance use and alcohol dependence or abuse. Sampling weights also used.	No Yes	Yes No	No Yes

(retrospective report)

Slutske et al., 2008	Australian Twin Registry: 836 twin pairs, 983 spouses and 2334 offspring (aged 18-39)	CoT	Alcoholism Structured Assessment for the Genetics of Alcoholism interview used to identify continuous (lifetime) symptom count of alcohol use disorder, and lifetime diagnosis of DSM-IV alcohol dependence.	Alcohol use disorder SSAGA used to identify continuous (lifetime) symptom count of alcohol use disorder	Demographics, other substance use and psychopathology in twins and spouses, educational attainment, parents age at birth of first child, church attendance, history of divorce, Plus sampling weights.	No	No	No		
Volk et al. 2007	1,213 win fathers from the VET registry, 862 mothers and 1,270 biological children	CoT	Alcohol Dependence DIS used to diagnose lifetime DSM-III-R AD Nicotine Dependence DIS used to diagnose lifetime DSM-III-R ND	Alcohol Dependence SSAGA used to diagnose lifetime DSM-III-R AD Nicotine Dependence SSAGA used to diagnose lifetime DSM-III-R ND	Maternal lifetime AD and ND. Mother reports of offspring ADHD and ODD. Offspring reported internalizing and externalizing disorders.	Unable to distinguish G from E Yes Bivariate analysis suggests risk is specific	-	No	-	Yes

Waldron et al., 2009	2 COT studies taken from the Australian Twin Registry: MATCH (617 twin pairs and 1643 adolescent offspring) and PACER (411 twin pairs and 756 adolescent offspring)	CoT	Alcoholism Structured Assessment for the Genetics of Alcoholism interview used to identify DSM-IV-R alcohol dependence and alcohol abuse	Externalizing problems Parent report CBCL (Achenbach, 2001) Internalizing problems Parent report CBCL (Achenbach, 2001) Total problems Composite of internalizing and externalizing	Yes	No	Yes
					Suggestive	No	No
					Yes	No	Yes

CoT=Children-of-Twins; ECoT=Extended Children-of-Twins; E- rGE=evocative rGE detected; P-rGE=Passive rGE identified; *in this table the 'environmental effect' column refers to the impact of parent phenotype on offspring phenotype

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